The following documentation is an electronically-submitted vendor response to an advertised solicitation from the *West Virginia Purchasing Bulletin* within the Vendor Self-Service portal at ***wvOASIS.gov***. As part of the State of West Virginia's procurement process, and to maintain the transparency of the bid-opening process, this documentation submitted online is publicly posted by the West Virginia Purchasing Division at ***WVPurchasing.gov*** with any other vendor responses to this solicitation submitted to the Purchasing Division in hard copy format.

Header 1

List View

General Information | Contact | Default Values | Discount | Document Information | Clarification Request

Procurement Folder: 999526
Procurement Type: Central Master Agreement
Vendor ID: 000000102111
Legal Name: CHANGE HEALTHCARE PHARMACY SOLUTIONS INC
Alias/DBA:
Total Bid: $2,246,694.84
Response Date: 05/18/2022
Response Time: 14:58
Responded By User ID: BizDev
First Name: Biz
Last Name: Dev
Email: Pba_bizdev@changehea
Phone: 207-622-7153

SO Doc Code: CRFQ
SO Dept: 0511
SO Doc ID: BMS2200000002
Published Date: 5/3/22
Close Date: 5/19/22
Close Time: 13:30
Status: Closed
Solicitation Description: PDL/PPL/HCPADL/SMAC SERVICES
Total of Header Attachments: 1
Total of All Attachments: 1

Department of Administration
Purchasing Division
2019 Washington Street East
Post Office Box 50130
Charleston, WV 25305-0130

State of West Virginia
Solicitation Response

Proc Folder:	999526
Solicitation Description:	PDL/PPL/HCPADL/SMAC SERVICES
Proc Type:	Central Master Agreement

Solicitation Closes	Solicitation Response	Version
2022-05-19 13:30	SR 0511 ESR05182200000007281	1

VENDOR

000000102111
CHANGE HEALTHCARE PHARMACY SOLUTIONS INC

Solicitation Number: CRFQ 0511 BMS2200000002

Total Bid: 2246694.839999999850988388061 **Response Date:** 2022-05-18 **Response Time:** 14:58:04

Comments:

FOR INFORMATION CONTACT THE BUYER
Crystal G Hustead
(304) 558-2402
crystal.g.hustead@wv.gov

Vendor
Signature X **FEIN#** **DATE**

All offers subject to all terms and conditions contained in this solicitation

Line	Comm Ln Desc	Qty	Unit Issue	Unit Price	Ln Total Or Contract Amount
1	PDL/PPL/HCPADL/ SMAC Startup Costs-Year 1				0.00

Comm Code	Manufacturer	Specification	Model #
85131701			

Commodity Line Comments:

Extended Description:

Lump Sum Cost for Initial Startup Costs
2 Month Startup.
Service Period: 01/01/2023-02/28/2023.

Line	Comm Ln Desc	Qty	Unit Issue	Unit Price	Ln Total Or Contract Amount
2	Annual Not To Exceed Costs-Year 1				512357.53

Comm Code	Manufacturer	Specification	Model #
85131701			

Commodity Line Comments:

Extended Description:

Annual Not To Exceed Costs-Year 1 (10 Months)
Service Period: 03/01/2023-12/31/2023

Line	Comm Ln Desc	Qty	Unit Issue	Unit Price	Ln Total Or Contract Amount
3	Additional Services Hourly Rate-Year 1				17492.49

Comm Code	Manufacturer	Specification	Model #
85131701			

Commodity Line Comments:

Extended Description:

Additional Services (all inclusive hourly rate) X 100 (Estimated) (See Section 4.1.26)-l Year One (1) Hourly Rate (10 months).
Service Period: 03/01/2023-12/31/2023

Line	Comm Ln Desc	Qty	Unit Issue	Unit Price	Ln Total Or Contract Amount
4	Annual Not To Exceed Costs-Year 2				537728.25

Comm Code	Manufacturer	Specification	Model #
85131701			

Commodity Line Comments:

Extended Description:

Annual Not To Exceed Costs-Year 2 (Optional Renewal Year 1) (12 Months)
Service Period: 01/01/2024-12/31/2024

Line	Comm Ln Desc	Qty	Unit Issue	Unit Price	Ln Total Or Contract Amount
5	Additional Services Hourly Rate-Year 2				18017.26

Comm Code	Manufacturer	Specification	Model #
85131701			

Commodity Line Comments:

Extended Description:

Additional Services Year 2 (Optional Renewal Year 1) (all inclusive hourly rate) X 100 (Estimated) (See Section 4.1.26).
Service Period: 01/01/2024-12/31/2024

Line	Comm Ln Desc	Qty	Unit Issue	Unit Price	Ln Total Or Contract Amount
6	Annual Not To Exceed Costs-Year 3				553560.10

Comm Code	Manufacturer	Specification	Model #
85131701			

Commodity Line Comments:

Extended Description:

Annual Not To Exceed Costs-Year 3 (Optional Renewal Year 2) (12 Months)
Service Period: 01/01/2025-12/31/2025

Line	Comm Ln Desc	Qty	Unit Issue	Unit Price	Ln Total Or Contract Amount
7	Additional Services Hourly Rate-Year 3				18557.78

Comm Code	Manufacturer	Specification	Model #
85131701			

Commodity Line Comments:

Extended Description:

Additional Services Year 3 (Optional Renewal Year 2) (all inclusive hourly rate) X 100 (Estimated) (See Section 4.1.26).
Service Period: 01/01/2025-12/31/2025

Line	Comm Ln Desc	Qty	Unit Issue	Unit Price	Ln Total Or Contract Amount
8	Annual Not To Exceed Costs-Year 4				569866.91

Comm Code	Manufacturer	Specification	Model #
85131701			

Commodity Line Comments:

Extended Description:

Annual Not To Exceed Costs-Year 4 (Optional Renewal Year 3) (12 Months)
Service Period: 01/01/2026-12/31/2026

Line	Comm Ln Desc	Qty	Unit Issue	Unit Price	Ln Total Or Contract Amount
9	Additional Services Hourly Rate-Year 4				19114.52

Comm Code	Manufacturer	Specification	Model #
85131701			

Commodity Line Comments:

Extended Description:

Additional Services Year 4 (Optional Renewal Year 3) (all inclusive hourly rate) X 100 (Estimated) (See Section 4.1.26).
Service Period: 01/01/2026-12/31/2026

West Virginia Bureau of Medical Services

PDL, PPL, HCPADL, and SMAC Services
RFQ CRFQ-051-BMS2200000002-1

May 18, 2022

Change Healthcare Pharmacy Solutions, Inc.
45 Commerce Drive
Augusta, ME 04330

CHANGE HEALTHCARE

PO Box 1090
Augusta, Maine, 04332-1090
www.changehealthcare.com

Tel: 207.622.7153
800.832.9672
Fax: 207.623.5125

May 18, 2022

Crystal Hustead
Department of Administration, Purchasing Division
2019 Washington Street East
Charleston, WV 25305-0130

RE: West Virginia Bureau of Medical Services PDL, PPL, HCPADL, and SMAC Services, CRFQ-051-BMS2200000002-1

Dear Ms. Hustead:

On behalf of Change Healthcare's Medicaid Pharmacy Benefits Solutions (PBS) division, Change Healthcare Pharmacy Solutions, Inc. I am pleased to present West Virginia Department of Health and Human Services, Bureau of Medical Services, hereinafter referred to as "BMS," with our response to the Request for Quote (RFQ) CRFQ-051-BMS2200000002-1.

Change Healthcare has been building positive relationships with the State of West Virginia for many years. We have successfully managed the preferred drug list (PDL), State Maximum Allowable Cost (SMAC) program and have provided rebate pricing files for the West Virginia Medicaid Fee for Service pharmacy benefit population since 2015. In 2019 Change Healthcare was successfully re-awarded this contract and as recently as February 2021 was awarded a one-year contract extension on this work.

Change Healthcare looks forward to continuing our relationship with BMS as we support you and the members of West Virginia.

We thank you for your time and consideration of our West Virginia Bureau of Medical Services RFQ, and we look forward to continuing our relationship with West Virginia. We are available to answer any questions you might have, provide any additional information you might request, and work with the BMS staff in the future.

Sincerely

Dan Hardin, Senior Vice President and General Manager
Pharmacy Benefit Solutions
45 Commerce Drive, Suite 5
Augusta, ME 04330
Office: (207) 622-7153 x 71127
Mobile: (630) 300-4407

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INSTRUCTIONS TO VENDORS SUBMITTING BIDS

1. REVIEW DOCUMENTS THOROUGHLY: The attached documents contain a solicitation for bids. Please read these instructions and all documents attached in their entirety. These instructions provide critical information about requirements that if overlooked could lead to disqualification of a Vendor's bid. All bids must be submitted in accordance with the provisions contained in these instructions and the Solicitation. Failure to do so may result in disqualification of Vendor's bid.

2. MANDATORY TERMS: The Solicitation may contain mandatory provisions identified by the use of the words "must," "will," and "shall." Failure to comply with a mandatory term in the Solicitation will result in bid disqualification.

3. PREBID MEETING: The item identified below shall apply to this Solicitation.

   ☑ A pre-bid meeting will not be held prior to bid opening

   ☐ A MANDATORY PRE-BID meeting will be held at the following place and time:

   All Vendors submitting a bid must attend the mandatory pre-bid meeting. Failure to attend the mandatory pre-bid meeting shall result in disqualification of the Vendor's bid. No one individual is permitted to represent more than one vendor at the pre-bid meeting. Any individual that does attempt to represent two or more vendors will be required to select one vendor to which the individual's attendance will be attributed. The vendors not selected will be deemed to have not attended the pre-bid meeting unless another individual attended on their behalf.

   An attendance sheet provided at the pre-bid meeting shall serve as the official document verifying attendance. Any person attending the pre-bid meeting on behalf of a Vendor must list on the attendance sheet his or her name and the name of the Vendor he or she is representing.

   Additionally, the person attending the pre-bid meeting should include the Vendor's E-Mail address, phone number, and Fax number on the attendance sheet. It is the Vendor's responsibility to locate the attendance sheet and provide the required information. Failure to complete the attendance sheet as required may result in disqualification of Vendor's bid.

   All Vendors should arrive prior to the starting time for the pre-bid. Vendors who arrive after the starting time but prior to the end of the pre-bid will be permitted to sign in but are charged with knowing all matters discussed at the pre-bid.

   Questions submitted at least five business days prior to a scheduled pre-bid will be discussed at the pre-bid meeting if possible. Any discussions or answers to questions at the pre-bid meeting are preliminary in nature and are non-binding. Official and binding answers to questions will be published in a written addendum to the Solicitation prior to bid opening.

4. VENDOR QUESTION DEADLINE: Vendors may submit questions relating to this Solicitation to the Purchasing Division. Questions must be submitted in writing. All questions must be submitted on or before the date listed below and to the address listed below to be considered. A written response will be published in a Solicitation addendum if a response is possible and appropriate. Non-written discussions, conversations, or questions and answers regarding this Solicitation are preliminary in nature and are nonbinding.

   Submitted emails should have the solicitation number in the subject line.

   Question Submission Deadline: May 9, 2022 at 10:00 AM ET

   Submit Questions to: Crystal Hustead
   2019 Washington Street, East Charleston, WV 25305
   Fax: (304) 558-3970
   Email: crystal.g.hustead@wv.gov

5. VERBAL COMMUNICATION: Any verbal communication between the Vendor and any State personnel is not binding, including verbal communication at the mandatory pre-bid conference. Only information issued in writing and added to the Solicitation by an official written addendum by the Purchasing Division is binding.

6. BID SUBMISSION: All bids must be submitted on or before the date and time of the bid opening listed in section 7 below. Vendors can submit bids electronically through wvOASIS, in paper form delivered to the Purchasing Division at the address listed below either in person or by courier, or in facsimile form by faxing to the Purchasing Division at the number listed below. Notwithstanding the foregoing, the Purchasing Division may prohibit the submission of bids electronically through wvOASIS at its sole discretion. Such a prohibition will be contained and communicated in the wvOASIS system resulting in the Vendor's inability to submit bids through wvOASIS. The Purchasing Division will not accept bids, modification of bids, or addendum acknowledgment forms via email. Bids submitted in paper or facsimile form must contain a signature. Bids submitted in wvOASIS are deemed to be electronically signed.

   Any bid received by the Purchasing Division staff is considered to be in the possession of the Purchasing Division and will not be returned for any reason.

   For Request for Proposal ("RFP") Responses Only: Submission of a response to a Request for Proposal is not permitted in wvOASIS. In the event that Vendor is responding to a request for proposal, the Vendor shall submit one original technical and one original cost proposal prior to the bid opening date and time identified in Section 7 below, plus n/a convenience copies of each to the Purchasing Division at the address shown below. Additionally, the Vendor should clearly identify and segregate the cost proposal from the technical proposal in a separately sealed envelope.

   Bid Delivery Address and Fax Number:
   Department of Administration, Purchasing Division 2019 Washington Street East
   Charleston, WV 25305-0130
   Fax: 304-558-3970

A bid submitted in paper or facsimile form should contain the information listed below on the face of the submission envelope or fax cover sheet. Otherwise, the bid may be rejected by the Purchasing Division.

VENDOR NAME:
BUYER: Crystal Hustead
SOLICITATION NO.: CRFQ BMS2200000002
BID OPENING DATE: May 19, 2022
BID OPENING TIME: 1:30 PM ET
FAX NUMBER: 304-558-3970

7. BID OPENING: Bids submitted in response to this Solicitation will be opened at the location identified below on the date and time listed below. Delivery of a bid after the bid opening date and time will result in bid disqualification. For purposes of this Solicitation, a bid is considered delivered when confirmation of delivery is provided by wvOASIS (in the case of electronic submission) or when the bid is time stamped by the official Purchasing Division time clock (in the case of hand delivery).

   Bid Opening Date and Time: May 19, 2022 at 1:30 PM ET

   Bid Opening Location: Department of Administration, Purchasing Division
   2019 Washington Street East
   Charleston, WV 25305-0130

8. ADDENDUM ACKNOWLEDGEMENT: Changes or revisions to this Solicitation will be made by an official written addendum issued by the Purchasing Division. Vendor should acknowledge receipt of all addenda issued with this Solicitation by completing an Addendum Acknowledgment Form, a copy of which is included herewith. Failure to acknowledge addenda may result in bid disqualification. The addendum acknowledgement should be submitted with the bid to expedite document processing.

9. BID FORMATTING: Vendor should type or electronically enter the information onto its bid to prevent errors in the evaluation. Failure to type or electronically enter the information may result in bid disqualification.

10. ALTERNATE MODEL OR BRAND: Unless the box below is checked, any model, brand, or specification listed in this Solicitation establishes the acceptable level of quality only and is not intended to reflect a preference for, or in any way favor, a particular brand or vendor. Vendors may bid alternates to a listed model or brand provided that the alternate is at least equal to the model or brand and complies with the required specifications. The equality of any alternate being bid shall be determined by the State at its sole discretion. Any Vendor bidding an alternate model or brand should clearly identify the alternate items in its bid and should include manufacturer's specifications, industry literature, and/or any other relevant documentation demonstrating the equality of the alternate items. Failure to provide information for alternate items may be grounds for rejection of a Vendor's bid.

☐ This Solicitation is based upon a standardized commodity established under W. Va. Code§ SA-3-61. Vendors are expected to bid the standardized commodity identified. Failure to bid the standardized commodity will result in your firm's bid being rejected.

11. EXCEPTIONS AND CLARIFICATIONS: The Solicitation contains the specifications that shall form the basis of a contractual agreement. Vendor shall clearly mark any exceptions, clarifications, or other proposed modifications in its bid. Exceptions to, clarifications of, or modifications of a requirement or term and condition of the Solicitation may result in bid disqualification.

12. COMMUNICATION LIMITATIONS: fu accordance with West Virginia Code of State Rules §148-1-6.6, communication with the State of West Virginia or any of its employees regarding this Solicitation during the solicitation, bid, evaluation or award periods, except through the Purchasing Division, is strictly prohibited without prior Purchasing Division approval. Purchasing Division approval for such communication is implied for all agency delegated and exempt purchases.

13. REGISTRATION: Prior to Contract award, the apparent successful Vendor must be properly registered with the West Virginia Purchasing Division and must have paid the $125 fee, if applicable.

14. UNIT PRICE: Unit prices shall prevail in cases of a discrepancy in the Vendor's bid.

15. PREFERENCE: Vendor Preference may be requested in purchases of motor vehicles or construction and maintenance equipment and machinery used in highway and other infrastructure projects. Any request for preference must be submitted in writing with the bid, must specifically identify the preference requested with reference to the applicable subsection of West Virginia Code§ SA-3-37, and must include with the bid any information necessary to evaluate and confirm the applicability of the requested preference. A request form to help facilitate the request can be found at: www.state.wv.us/admin/purchase/vrcNenpref.pdf.

15A. RECIPROCAL PREFERENCE: The State of West Virginia applies a reciprocal preference to all solicitations for commodities and printing in accordance with W. Va. Code§ SA-3-37(b). In effect, non-resident vendors receiving a preference in their home states, will see that same preference granted to West Virginia resident vendors bidding against them in West Virginia. Any request for reciprocal preference must include with the bid any information necessary to evaluate and confirm the applicability of the preference. A request form to help facilitate the request can be found at: www.state.wv.us/admin/purchase/vrcNenpref.pdf.

16. SMALL, WOMEN-OWNED, OR MINORITY-OWNED BUSINESSES: For any solicitations publicly advertised for bid, in accordance with West Virginia Code §5A-3-37(a)(7) and W. Va. CSR§ 148-22-9, any non-resident vendor certified as a small, women- owned, or minority-owned business under W. Va. CSR § 148-22-9 shall be provided the same preference made available to any resident vendor. Any non-resident small, women-owned, or minority-owned business must identify itself as such in writing, must submit that writing to the Purchasing Division with its bid, and must be properly

certified under W. Va. CSR§ 148-22-9 prior to contract award to receive the preferences made available to resident vendors. Preference for a non-resident small, women-owned, or minority owned business shall be applied in accordance with W. Va. CSR§ 148-22-9.

17. WAIVER OF MINOR IRREGULARITIES: The Director reserves the right to waive minor irregularities in bids or specifications in accordance with West Virginia Code of State Rules§ 148-1-4.6.

18. ELECTRONIC FILE ACCESS RESTRICTIONS: Vendor must ensure that its submission in wvOASIS can be accessed and viewed by the Purchasing Division staff immediately upon bid opening. The Purchasing Division will consider any file that cannot be immediately accessed and viewed at the time of the bid opening (such as, encrypted files, password protected files, or incompatible files) to be blank or incomplete as context requires and are therefore unacceptable. A vendor will not be permitted to unencrypt files, remove password protections, or resubmit documents after bid opening to make a file viewable if those documents are required with the bid. A Vendor may be required to provide document passwords or remove access restrictions to allow the Purchasing Division to print or electronically save documents provided that those documents are viewable by the Purchasing Division prior to obtaining the password or removing the access restriction.

19. NON-RESPONSIBLE: The Purchasing Division Director reserves the right to reject the bid of any vendor as Non-Responsible in accordance with W. Va. Code of State Rules§ 148-1-5.3, when the Director determines that the vendor submitting the bid does not have the capability to fully perform or lacks the integrity and reliability to assure good-faith performance."

20. ACCEPTANCE/REJECTION: The State may accept or reject any bid in whole, or in part in accordance with W. Va. Code of State Rules§ 148-1-4.5. and§ 148-1-6.4.b."

21. YOUR SUBMISSION IS A PUBLIC DOCUMENT: Vendor's entire response to the Solicitation and the resulting Contract are public documents. As public documents, they will be disclosed to the public following the bid/proposal opening or award of the contract, as required by the competitive bidding laws of West Virginia Code§§ 5A-3-l et seq., 5-22-1 et seq., and 50-1-1 et seq. and the Freedom of Information Act West Virginia Code§§ 29B-1-1 et seq.

    DO NOT SUBMIT MATERIAL YOU CONSIDER TO BE CONFIDENTIAL, A TRADE SECRET, OR OTHERWISE NOT SUBJECT TO PUBLIC DISCLOSURE.

    Submission of any bid, proposal, or other document to the Purchasing Division constitutes your explicit consent to the subsequent public disclosure of the bid, proposal, or document. The Purchasing Division will disclose any document labeled "confidential," "proprietary," "trade secret," "private," or labeled with any other claim against public disclosure of the documents, to include any "trade secrets" as defined by West Virginia Code§ 47-22-1 et seq. All submissions are subject to public disclosure without notice.

22. WITH THE BID REQUIREMENTS: In instances where these specifications require documentation or other information with the bid, and a vendor fails to provide it with the

bid, the Director of the Purchasing Division reserves the right to request those items after bid opening and prior to contract award pursuant to the authority to waive minor irregularities in bids or specifications under W. Va. CSR § 148-1-4.6. This authority does not apply to instances where state law mandates receipt with the bid.

23. EMAIL NOTIFICATION OF AWARD: The Purchasing Division will attempt to provide bidders with e-mail notification of contract award when a solicitation that the bidder participated in has been awarded. For notification purposes, bidders must provide the Purchasing Division with a valid email address in the bid response. Bidders may also monitor wvOASIS or the Purchasing Division's website to determine when a contract has been awarded.

24. ISRAEL BOYCOTT CERTIFICATION: Vendor's act of submitting a bid in response to this solicitation shall be deemed a certification from bidder to the State that bidder is not currently engaged in, and will not for the duration of the contract, engage in a boycott of Israel. This certification is required by W. Va. Code§ SA-3-63.

GENERAL TERMS AND CONDITIONS

Change Healthcare Pharmacy Solutions, Inc. (Change Healthcare) submits the following exceptions that relate to the State of West Virginia's RFQ Terms and Conditions. If awarded the business, Change Healthcare looks forward to negotiating a mutually agreeable Agreement with the State of West Virginia Bureau of Medical Services. Change Healthcare's initial comments on the State's terms and conditions are outlined below in response to Sections 8, 27, 30, and 36.

1. **CONTRACTUAL AGREEMENT**: Issuance of an Award Document signed by the Purchasing Division Director, or his designee, and approved as to form by the Attorney General's office constitutes acceptance by the State of this Contract made by and between the State of West Virginia and the Vendor. Vendor's signature on its bid, or on the Contract if the Contract is not the result of a bid solicitation, signifies Vendor's agreement to be bound by and accept the terms and conditions contained in this Contract.

2. **DEFINITIONS**: As used in this Solicitation/Contract, the following terms shall have the meanings attributed to them below. Additional definitions may be found in the specifications included with this Solicitation/Contract.

2.1. **"Agency"** or **"Agencies"** means the agency, board, commission, or other entity of the State of West Virginia that is identified on the first page of the Solicitation or any other public entity seeking to procure goods or services under this Contract.

2.2. **"Bid"** or **"Proposal"** means the vendors submitted response to this solicitation.

2.3. **"Contract"** means the binding agreement that is entered into between the State and the Vendor to provide the goods or services requested in the Solicitation.

2.4. **"Director"** means the Director of the West Virginia Department of Administration, Purchasing Division.

2.5. **"Purchasing Division"** means the West Virginia Department of Administration, Purchasing Division.

2.6. **"Award Document"** means the document signed by the Agency and the Purchasing Division, and approved as to form by the Attorney General, that identifies the Vendor as the contract holder.

2.7. **"Solicitation"** means the official notice of an opportunity to supply the State with goods or services that is published by the Purchasing Division.

2.8. **"State"** means the State of West Virginia and/or any of its agencies, commissions, boards, etc. as context requires.

2.9. **"Vendor"** or **"Vendors"** means any entity submitting a bid in response to the Solicitation, the entity that has been selected as the lowest responsible bidder, or the entity that has been awarded the Contract as context requires.

3. **CONTRACT TERM; RENEWAL; EXTENSION**: The term of this Contract shall be determined in accordance with the category that has been identified as applicable to this Contract below:

☑ **Term Contract**

Initial Contract Term: The Initial Contract Term will be for a period of one (1) Year. The Initial Contract Term becomes effective on the effective start date listed on the first page of this Contract and the Initial Contract Term ends on the effective end date also shown on the first page of this Contract.

Renewal Term: This Contract may be renewed upon the mutual written consent of the Agency, and the Vendor, with approval of the Purchasing Division and the Attorney General's office (Attorney General approval is as to form only). Any request for renewal should be delivered to the Agency and then submitted to the Purchasing Division thirty (30) days prior to the expiration date of the initial contract term or appropriate renewal term. A Contract renewal shall be in accordance with the terms and conditions of the original contract. Unless otherwise specified below, renewal of this Contract is limited to three (3) successive one (1) year periods or multiple renewal periods of less than one year, provided that the multiple renewal periods do not exceed the total number of months available in all renewal years combined. Automatic renewal of this Contract is prohibited. Renewals must be approved by the Vendor, Agency, Purchasing Division and Attorney General's office (Attorney General approval is as to form only)

☐ **Alternate Renewal Term** - This contract may be renewed for____ successive ___ year periods or shorter periods provided that they do not exceed the total number of months contained in all available renewals. Automatic renewal of this Contract is prohibited. Renewals must be approved by the Vendor, Agency, Purchasing Division and Attorney General's office (Attorney General approval is as to form only)

Delivery Order Limitations: In the event that this contract permits delivery orders, a delivery order may only be issued during the time this Contract is in effect. Any delivery order issued within one year of the expiration of this Contract shall be effective for one year from the date the delivery order is issued. No delivery order may be extended beyond one year after this Contract has expired.

☐ **Fixed Period Contract:** This Contract becomes effective upon Vendor's receipt of the notice to proceed and must be completed within _____ days.

☐ **Fixed Period Contract with Renewals**: This Contract becomes effective upon Vendor's receipt of the notice to proceed and part of the Contract more fully described in the attached specifications must be completed within _____ days. Upon completion of the work covered by the preceding sentence, the vendor agrees that:

☐ the contract will continue for _____ years;

☐ the contract may be renewed for _____ successive _____ year periods or shorter periods provided that they do not exceed the total number of months contained in all available renewals. Automatic renewal of this Contract is prohibited. Renewals must be approved by the Vendor, Agency, Purchasing Division and Attorney General's Office (Attorney General approval is as to form only).

☐ **One-Time Purchase:** The term of this Contract shall run from the issuance of the Award Document until all of the goods contracted for have been delivered, but in no event will this Contract extend for more than one fiscal year.

☐ **Other:** Contract Term specified in _____

4. **AUTHORITY TO PROCEED**: Vendor is authorized to begin performance of this contract on the date of encumbrance listed on the front page of the Award Document unless either the box for "Fixed Period Contract" or "Fixed Period Contract with Renewals" has been checked in Section 3 above. If either "Fixed Period Contract" or "Fixed Period Contract with Renewals" has been checked, Vendor must not begin work until it receives a separate notice to proceed from the State. The notice to proceed will then be incorporated into the Contract via change order to memorialize the official date that work commenced.

5. **QUANTITIES**: The quantities required under this Contract shall be determined in accordance with the category that has been identified as applicable to this Contract below.

☑ **Open End Contract:** Quantities listed in this Solicitation/Award Document are approximations only, based on estimates supplied by the Agency. It is understood and agreed that the Contract shall cover the quantities actually ordered for delivery during the term of the Contract, whether more or less than the quantities shown.

☐ **Service:** The scope of the service to be provided will be more clearly defined in the specifications included herewith.

☐ **Combined Service and Goods:** The scope of the service and deliverable goods to be provided will be more clearly defined in the specifications included herewith.

☐ **One-Time Purchase:** This Contract is for the purchase of a set quantity of goods that are identified in the specifications included herewith. Once those items have been delivered, no additional goods may be procured under this Contract without an appropriate change order approved by the Vendor, Agency, Purchasing Division, and Attorney General's office.

6. **EMERGENCY PURCHASES**: The Purchasing Division Director may authorize the Agency to purchase goods or services in the open market that Vendor would otherwise provide under this Contract if those goods or services are for immediate or expedited delivery in an emergency. Emergencies shall include, but are not limited to, delays in transportation or an unanticipated increase in the volume of work. An emergency purchase in the open market, approved by the Purchasing Division Director, shall not

constitute of breach of this Contract and shall not entitle the Vendor to any form of compensation or damages. This provision does not excuse the State from fulfilling its obligations under a One-Time Purchase contract.

7. **REQUIRED DOCUMENTS**: All of the items checked in this section must be provided to the Purchasing Division by the Vendor as specified:

☐ **BID BOND (Construction Only):** Pursuant to the requirements contained in W. Va. Code§ 5-22-l(c), All Vendors submitting a bid on a construction project shall furnish a valid bid bond in the amount of five percent (5%) of the total amount of the bid protecting the State of West Virginia. The bid bond must be submitted with the bid.

☐ **PERFORMANCE BOND:** The apparent successful Vendor shall provide a performance bond in the amount of 100% of the contract. The performance bond must be received by the Purchasing Division prior to Contract award.

☐ **LABOR/MATERIAL PAYMENT BOND:** The apparent successful Vendor shall provide a labor/material payment bond in the amount of 100% of the Contract value. The labor/material payment bond must be delivered to the Purchasing Division prior to Contract award.

In lieu of the Bid Bond, Performance Bond, and Labor/Material Payment Bond, the Vendor may provide certified checks, cashier's checks, or irrevocable letters of credit. Any certified check, cashier's check, or irrevocable letter of credit provided in lieu of a bond must be of the same amount and delivered on the same schedule as the bond it replaces. A letter of credit submitted in lieu of a performance and labor/material payment bond will only be allowed for projects under

$100,000. Personal or business checks are not acceptable. Notwithstanding the foregoing, West Virginia Code § 5-22-1 (d) mandates that a vendor provide a performance and labor/material payment bond for construction projects. Accordingly, substitutions for the performance and labor/material payment bonds for construction projects is not permitted.

☐ **MAINTENANCE BOND:** The apparent successful Vendor shall provide a two (2) year maintenance bond covering the roofing system. The maintenance bond must be issued and delivered to the Purchasing Division prior to Contract award.

☑ **LICENSE(S) /CERTIFICATIONS/ PERMITS:** In addition to anything required under the Section of the General Terms and Conditions entitled Licensing, the apparent successful Vendor shall furnish proof of the following licenses, certifications, and/or permits upon request and in a form acceptable to the State. The request may be prior to or after contract award at the State's sole discretion.

☑ Pharmacists (RPh or PharmD)

☑ Physicians (MD or DO)

☐

☐

The apparent successful Vendor shall also furnish proof of any additional licenses or certifications contained in the specifications regardless of whether or not that requirement is listed above.

8. INSURANCE: The apparent successful Vendor shall furnish proof of the insurance identified by a checkmark below and must include the State as an additional insured on each policy prior to Contract award. The insurance coverages identified below must be maintained throughout the life of this contract. Thirty (30) days prior to the expiration of the insurance policies, Vendor shall provide the Agency with proof that the insurance mandated herein has been continued. Vendor must also provide Agency with immediate notice of any changes in its insurance policies, including but not limited to, policy cancelation, policy reduction, or change in insurers. The apparent successful Vendor shall also furnish proof of any additional insurance requirements contained in the specifications prior to Contract award regardless of whether that insurance requirement is listed in this section.

Vendor must maintain:

☑ **Commercial General Liability Insurance** in at least an amount of: $1,000,000.00 per occurrence.

☑ **Automobile Liability Insurance** in at least an amount of: $1,000,000.00 per occurrence.

☑ **Professional/Malpractice/Errors and Omission Insurance** in at least an amount of: $1,000,000.00 per occurrence. Notwithstanding the forgoing, Vendor's are not required to list the State as an additional insured for this type of policy.

☐ **Commercial Crime and Third Party Fidelity Insurance** in an amount of: _____ per occurrence.

☑ **Cyber Liability Insurance** in an amount of: $1,000,000.00 per occurrence.

☐ **Builders Risk Insurance** in an amount equal to 100% of the amount of the Contract.

☐ **Pollution Insurance** in an amount of: _____ per occurrence.

☐ **Aircraft Liability** in an amount of: _____ per occurrence.

☑ ***THE STATE OF WV MUST BE LISTED AS ADDITIONAL INSURED ON INSURANCE CERTIFICATE

☑ ***CERTIFICATE HOLDER SHOULD READ AS FOLLOWS:

WVDHHR
350 CAPITOL ST, RM 251, CHARLESTON, WV 25301

☐

☐

Notwithstanding anything contained in this section to the contrary, the Director of the Purchasing Division reserves the right to waive the requirement that the State be named as an additional insured on one or more of the Vendor's insurance policies if the Director finds that doing so is in the State's best interest.

Change Healthcare's Professional Liability (E&O) and Cyber policies are included in one policy. The policy covers any third parties for our negligence, errors, etc., and as such, West Virginia would be covered as a third party. Change Healthcare would not name West Virginia as an additional insured on this policy. For General Liability and Auto, West Virginia can be named as an additional insured.

9. **WORKERS' COMPENSATION INSURANCE**: Vendor shall comply with laws relating to workers compensation, shall maintain workers' compensation insurance when required, and shall furnish proof of workers' compensation insurance upon request.

10. **[Reserved]**

11. **LIQUIDATED DAMAGES**: This clause shall in no way be considered exclusive and shall not limit the State or Agency's right to pursue any other available remedy. Vendor shall pay liquidated damages in the amount specified below or as described in the specifications:

    ☐ _____ for _____.

    ☐ Liquidated Damages Contained in the Specifications.

    ☑ Liquidated Damages Are Not Included in this Contract.

12. **ACCEPTANCE**: Vendor's signature on its bid, or on the certification and signature page, constitutes an offer to the State that cannot be unilaterally withdrawn, signifies that the product or service proposed by vendor meets the mandatory requirements contained in the Solicitation for that product or service, unless otherwise indicated, and signifies acceptance of the terms and conditions contained in the Solicitation unless otherwise indicated.

13. **PRICING**: The pricing set forth herein is firm for the life of the Contract, unless specified elsewhere within this Solicitation/Contract by the State. A Vendor's inclusion of price adjustment provisions in its bid, without an express authorization from the State in the Solicitation to do so, may result in bid disqualification. Notwithstanding the foregoing, Vendor must extend any publicly advertised sale price to the State and invoice at the lower of the contract price or the publicly advertised sale price.

14. **PAYMENT IN ARREARS**: Payments for goods/services will be made in arrears only upon receipt of a proper invoice, detailing the goods/services provided or receipt of the goods/services, whichever is later. Notwithstanding the foregoing, payments for software maintenance, licenses, or subscriptions may be paid annually in advance.

15. **PAYMENT METHODS**: Vendor must accept payment by electronic funds transfer and P-Card. (The State of West Virginia's Purchasing Card program, administered under

contract by a banking institution, processes payment for goods and services through state designated credit cards.)

16. **TAXES**: The Vendor shall pay any applicable sales, use, personal property or any other taxes arising out of this Contract and the transactions contemplated thereby. The State of West Virginia is exempt from federal and state taxes and will not pay or reimburse such taxes.

17. **ADDITIONAL FEES**: Vendor is not permitted to charge additional fees or assess additional charges that were not either expressly provided for in the solicitation published by the State of West Virginia, included in the Contract, or included in the unit price or lump sum bid amount that Vendor is required by the solicitation to provide. Including such fees or charges as notes to the solicitation may result in rejection of vendor's bid. Requesting such fees or charges be paid after the contract has been awarded may result in cancellation of the contract.

18. **FUNDING**: This Contract shall continue for the term stated herein, contingent upon funds being appropriated by the Legislature or otherwise being made available. In the event funds are not appropriated or otherwise made available, this Contract becomes void and of no effect beginning on July 1 of the fiscal year for which funding has not been appropriated or otherwise made available. If that occurs, the State may notify the Vendor that an alternative source of funding has been obtained and thereby avoid the automatic termination. Non-appropriation or non-funding shall not be considered an event of default.

19. **CANCELLATION**: The Purchasing Division Director reserves the right to cancel this Contract immediately upon written notice to the vendor if the materials or workmanship supplied do not conform to the specifications contained in the Contract. The Purchasing Division Director may also cancel any purchase or Contract upon 30 days written notice to the Vendor in accordance with West Virginia Code of State Rules§ 148-1-5.2.b.

20. **TIME**: Time is of the essence regarding all matters of time and performance in this Contract.

21. **APPLICABLE LAW**: This Contract is governed by and interpreted under West Virginia law without giving effect to its choice of law principles. Any information provided in specification manuals, or any other source, verbal or written, which contradicts or violates the West Virginia Constitution, West Virginia Code, or West Virginia Code of State Rules is void and of no effect.

22. **COMPLIANCE WITH LAWS**: Vendor shall comply with all applicable federal, state, and local laws, regulations and ordinances. By submitting a bid, Vendor acknowledges that it has reviewed, understands, and will comply with all applicable laws, regulations, and ordinances.

    SUBCONTRACTOR COMPLIANCE: Vendor shall notify all subcontractors providing commodities or services related to this Contract that as subcontractors, they too are required to comply with all applicable laws, regulations, and

ordinances. Notification under this provision must occur prior to the performance of any work under the contract by the subcontractor.

23. **ARBITRATION**: Any references made to arbitration contained in this Contract, Vendor's bid, or in any American Institute of Architects documents pertaining to this Contract are hereby deleted, void, and of no effect.

24. **MODIFICATIONS**: This writing is the parties' final expression of intent. Notwithstanding anything contained in this Contract to the contrary no modification of this Contract shall be binding without mutual written consent of the Agency, and the Vendor, with approval of the Purchasing Division and the Attorney General's office (Attorney General approval is as to form only). Any change to existing contracts that adds work or changes contract cost, and were not included in the original contract, must be approved by the Purchasing Division and the Attorney General's Office (as to form) prior to the implementation of the change or commencement of work affected by the change.

25. **WAIVER**: The failure of either party to insist upon a strict performance of any of the terms or provision of this Contract, or to exercise any option, right, or remedy herein contained, shall not be construed as a waiver or a relinquishment for the future of such term, provision, option, right, or remedy, but the same shall continue in full force and effect. Any waiver must be expressly stated in writing and signed by the waiving party.

26. **SUBSEQUENT FORMS**: The terms and conditions contained in this Contract shall supersede any and all subsequent terms and conditions which may appear on any form documents submitted by Vendor to the Agency or Purchasing Division such as price lists, order forms, invoices, sales agreements, or maintenance agreements, and includes internet websites or other electronic documents. Acceptance or use of Vendor's forms does not constitute acceptance of the terms and conditions contained thereon.

27. **ASSIGNMENT**: Neither this Contract nor any monies due, or to become due hereunder, may be assigned by the Vendor without the express written consent of the Agency, the Purchasing Division, the Attorney General's office (as to form only), and any other government agency or office that may be required to approve such assignments.

    Change Healthcare requests the right to transfer the Agreement based on stock sale, merger, or other corporate reorganization.

28. **WARRANTY**: The Vendor expressly warrants that the goods and/or services covered by this Contract will: (a) conform to the specifications, drawings, samples, or other description furnished or specified by the Agency; (b) be merchantable and fit for the purpose intended; and (c) be free from defect in material and workmanship.

29. **STATE EMPLOYEES**: State employees are not permitted to utilize this Contract for personal use and the Vendor is prohibited from permitting or facilitating the same.

30. **PRIVACY, SECURITY, AND CONFIDENTIALITY**: The Vendor agrees that it will not disclose to anyone, directly or indirectly, any such personally identifiable information or other confidential information gained from the Agency, unless the individual who is the subject of the information consents to the disclosure in writing or the disclosure is made

pursuant to the Agency's policies, procedures, and rules. Vendor further agrees to comply with the Confidentiality Policies and Information Security Accountability Requirements, set forth in http://www.state.wv.us/admin/purchase/privacy/default.html.

Change Healthcare requests mutual confidentiality provisions to cover Change Healthcare's confidential and proprietary information with standard protections and exclusions.

Change Healthcare requests for the carve out of PII and PHI from the definition of Confidential.

31. **YOUR SUBMISSION IS A PUBLIC DOCUMENT**: Vendor's entire response to the Solicitation and the resulting Contract are public documents. As public documents, they will be disclosed to the public following the bid/proposal opening or award of the contract, as required by the competitive bidding laws of West Virginia Code §§ 5A-3-1 et seq., 5-22-1 et seq., and 50-1-1 et seq. and the Freedom of Information Act West Virginia Code§§ 29B-l-I et seq.

    DO NOT SUBMIT MATERIAL YOU CONSIDER TO BE CONFIDENTIAL, A TRADE SECRET, OR OTHERWISE NOT SUBJECT TO PUBLIC DISCLOSURE.

    Submission of any bid, proposal, or other document to the Purchasing Division constitutes your explicit consent to the subsequent public disclosure of the bid, proposal, or document. The Purchasing Division will disclose any document labeled "confidential," "proprietary," "trade secret," "private," or labeled with any other claim against public disclosure of the documents, to include any "trade secrets" as defined by West Virginia Code§ 47-22-1 et seq. All submissions are subject to public disclosure without notice.

32. **LICENSING**: In accordance with West Virginia Code of State Rules§ 148-1-6.1.e, Vendor must be licensed and in good standing in accordance with any and all state and local laws and requirements by any state or local agency of West Virginia, including, but not limited to, the West Virginia Secretary of State's Office, the West Virginia Tax Department, West Virginia Insurance Commission, or any other state agency or political subdivision. Obligations related to political subdivisions may include, but are not limited to, business licensing, business and occupation taxes, inspection compliance, permitting, etc. Upon request, the Vendor must provide all necessary releases to obtain information to enable the Purchasing Division Director or the Agency to verify that the Vendor is licensed and in good standing with the above entities.

    SUBCONTRACTOR COMPLIANCE: Vendor shall notify all subcontractors providing commodities or services related to this Contract that as subcontractors, they too are required to be licensed, in good standing, and up-to-date on all state and local obligations as described in this section. Obligations related to political subdivisions may include, but are not limited to, business licensing, business and occupation taxes, inspection compliance, permitting, etc. Notification under this provision must occur prior to the performance of any work under the contract by the subcontractor.

33. **ANTITRUST**: In submitting a bid to, signing a contract with, or accepting a Award Document from any agency of the State of West Virginia, the Vendor agrees to convey, sell, assign, or transfer to the State of West Virginia all rights, title, and interest in and to all causes of action it may now or hereafter acquire under the antitrust laws of the United States and the State of West Virginia for price fixing and/or unreasonable restraints of trade relating to the particular commodities or services purchased or acquired by the State of West Virginia. Such assignment shall be made and become effective at the time the purchasing agency tenders the initial payment to Vendor.

34. **VENDOR CERTIFICATIONS**: By signing its bid or entering into this Contract, Vendor certifies (1) that its bid or offer was made without prior understanding, agreement, or connection with any corporation, firm, limited liability company, partnership, person or entity submitting a bid or offer for the same material, supplies, equipment or services; (2) that its bid or offer is in all respects fair and without collusion or fraud; (3) that this Contract is accepted or entered into without any prior understanding, agreement, or connection to any other entity that could be considered a violation of law; and (4) that it has reviewed this Solicitation in its entirety; understands the requirements, terms and conditions, and other information contained herein.

    Vendor's signature on its bid or offer also affirms that neither it nor its representatives have any interest, nor shall acquire any interest, direct or indirect, which would compromise the performance of its services hereunder. Any such interests shall be promptly presented in detail to the Agency. The individual signing this bid or offer on behalf of Vendor certifies that he or she is authorized by the Vendor to execute this bid or offer or any documents related thereto on Vendor's behalf; that he or she is authorized to bind the Vendor in a contractual relationship; and that, to the best of his or her knowledge, the Vendor has properly registered with any State agency that may require registration.

35. **VENDOR RELATIONSHIP**: The relationship of the Vendor to the State shall be that of an independent contractor and no principal-agent relationship or employer-employee relationship is contemplated or created by this Contract. The Vendor as an independent contractor is solely liable for the acts and omissions of its employees and agents. Vendor shall be responsible for selecting, supervising, and compensating any and all individuals employed pursuant to the terms of this Solicitation and resulting contract. Neither the Vendor, nor any employees or subcontractors of the Vendor, shall be deemed to be employees of the State for any purpose whatsoever. Vendor shall be exclusively responsible for payment of employees and contractors for all wages and salaries, taxes, withholding payments, penalties, fees, fringe benefits, professional liability insurance premiums, contributions to insurance and pension, or other deferred compensation plans, including but not limited to, Workers' Compensation and Social Security obligations, licensing fees, etc. and the filing of all necessary documents, forms, and returns pertinent to all of the foregoing.

    Vendor shall hold harmless the State, and shall provide the State and Agency with a defense against any and all claims including, but not limited to, the foregoing payments,

withholdings, contributions, taxes, Social Security taxes, and employer income tax returns.

36. **INDEMNIFICATION**: The Vendor agrees to indemnify, defend, and hold harmless the State and the Agency, their officers, and employees from and against: (1) Any claims or losses for services rendered by any subcontractor, person, or firm performing or supplying services, materials, or supplies in connection with the performance of the Contract; (2) Any claims or losses resulting to any person or entity injured or damaged by the Vendor, its officers, employees, or subcontractors by the publication, translation, reproduction, delivery, performance, use, or disposition of any data used under the Contract in a manner not authorized by the Contract, or by Federal or State statutes or regulations; and (3) Any failure of the Vendor, its officers, employees, or subcontractors to observe State and Federal laws including, but not limited to, labor and wage and hour laws.

Change Healthcare requests to limit the indemnity obligation to third-party claims resulting from (1) Change Healthcare's fraud or intentional misconduct, or (2) injuries to person or tangible property damage while Change Healthcare is at the State's premises performing the services. Change Healthcare also requests inclusion of our standard indemnification requirements and exclusions.

37. **NO DEBT CERTIFICATION**: In accordance with West Virginia Code§§ 5A-3-10a and 5-22-1(i), the State is prohibited from awarding a contract to any bidder that owes a debt to the State or a political subdivision of the State. By submitting a bid, or entering into a contract with the State, Vendor is affirming that (1) for construction contracts, the Vendor is not in default on any monetary obligation owed to the state or a political subdivision of the state, and (2) for all other contracts, neither the Vendor nor any related party owe a debt as defined above, and neither the Vendor nor any related party are in employer default as defined in the statute cited above unless the debt or employer default is permitted under the statute.

38. **CONFLICT OF INTEREST**: Vendor, its officers or members or employees, shall not presently have or acquire an interest, direct or indirect, which would conflict with or compromise the performance of its obligations hereunder. Vendor shall periodically inquire of its officers, members and employees to ensure that a conflict of interest does not arise. Any conflict of interest discovered shall be promptly presented in detail to the Agency.

39. **REPORTS**: Vendor shall provide the Agency and/or the Purchasing Division with the following reports identified by a checked box below:

☑ Such reports as the Agency and/or the Purchasing Division may request. Requested reports may include, but are not limited to, quantities purchased, agencies utilizing the contract, total contract expenditures by agency, etc.

☐ Quarterly reports detailing the total quantity of purchases in units and dollars, along with a listing of purchases by agency. Quarterly reports should be delivered to the Purchasing Division via email at purchasing.division@wy.gov.

40. **BACKGROUND CHECK**: In accordance with W. Va. Code§ 15-2D-3, the State reserves the right to prohibit a service provider's employees from accessing sensitive or critical information or to be present at the Capitol complex based upon results addressed from a criminal background check. Service providers should contact the West Virginia Division of Protective Services by phone at (304) 558-9911 for more information.

41. **PREFERENCE FOR USE OF DOMESTIC STEEL PRODUCTS:** Except when authorized by the Director of the Purchasing Division pursuant to W. Va. Code § SA-3-56, no contractor may use or supply steel products for a State Contract Project other than those steel products made in the United States. A contractor who uses steel products in violation of this section may be subject to civil penalties pursuant to W. Va. Code § SA-3-56. As used in this section:

    a. "State Contract Project" means any erection or construction of, or any addition to, alteration of or other improvement to any building or structure, including, but not limited to, roads or highways, or the installation of any heating or cooling or ventilating plants or other equipment, or the supply of and materials for such projects, pursuant to a contract with the State of West Virginia for which bids were solicited on or after June 6, 2001.

    b. "Steel Products" means products rolled, formed, shaped, drawn, extruded, forged, cast, fabricated or otherwise similarly processed, or processed by a combination of two or more or such operations, from steel made by the open heath, basic oxygen, electric furnace, Bessemer or other steel making process.

    c. The Purchasing Division Director may, in writing, authorize the use of foreign steel products if:

        1. The cost for each contract item used does not exceed one tenth of one percent (.1%) of the total contract cost or two thousand five hundred dollars ($2,500.00), whichever is greater. For the purposes of this section, the cost is the value of the steel product as delivered to the project; or

        2. The Director of the Purchasing Division determines that specified steel materials are not produced in the United States in sufficient quantity or otherwise are not reasonably available to meet contract requirements.

42. **PREFERENCE FOR USE OF DOMESTIC ALUMINUM, GLASS, AND STEEL**: In Accordance with W. Va. Code§ 5-19-1 et seq., and W. Va. CSR§ 148-10-1 et seq., for every contract or subcontract, subject to the limitations contained herein, for the construction, reconstruction, alteration, repair, improvement or maintenance of public works or for the purchase of any item of machinery or equipment to be used at sites of public works, only domestic aluminum, glass or steel products shall be supplied unless the spending officer determines, in writing, after the receipt of offers or bids, (1) that the cost of domestic aluminum, glass or steel products is unreasonable or inconsistent with the public interest of the State of West Virginia, (2) that domestic aluminum, glass or steel products are not produced in sufficient quantities to meet the contract requirements, or (3) the available domestic aluminum, glass, or steel do not meet the

contract specifications. This provision only applies to public works contracts awarded in an amount more than fifty thousand dollars ($50,000) or public works contracts that require more than ten thousand pounds of steel products.

The cost of domestic aluminum, glass, or steel products may be unreasonable if the cost is more than twenty percent (20%) of the bid or offered price for foreign made aluminum, glass, or steel products. If the domestic aluminum, glass or steel products to be supplied or produced in a "substantial labor surplus area", as defined by the United States Department of Labor, the cost of domestic aluminum, glass, or steel products may be unreasonable if the cost is more than thirty percent (30%) of the bid or offered price for foreign made aluminum, glass, or steel products. This preference shall be applied to an item of machinery or equipment, as indicated above, when the item is a single unit of equipment or machinery manufactured primarily of aluminum, glass or steel, is part of a public works contract and has the sole purpose or of being a permanent part of a single public works project. This provision does not apply to equipment or machinery purchased by a spending unit for use by that spending unit and not as part of a single public works project.

All bids and offers including domestic aluminum, glass or steel products that exceed bid or offer prices including foreign aluminum, glass or steel products after application of the preferences provided in this provision may be reduced to a price equal to or lower than the lowest bid or offer price for foreign aluminum, glass or steel products plus the applicable preference. If the reduced bid or offer prices are made in writing and supersede the prior bid or offer prices, all bids or offers, including the reduced bid or offer prices, will be reevaluated in accordance with this rule.

43. **INTERESTED PARTY SUPPLEMENTAL DISCLOSURE**: W. Va. Code§ 6D-1-2 requires that for contracts with an actual or estimated value of at least $1 million, the Vendor must submit to the Agency a disclosure of interested parties prior to beginning work under this Contract. Additionally, the Vendor must submit a supplemental disclosure of interested parties reflecting any new or differing interested parties to the contract, which were not included in the original pre-work interested party disclosure, within 30 days following the completion or termination of the contract. A copy of that form is included with this solicitation or can be obtained from the WV Ethics Commission. This requirement does not apply to publicly traded companies listed on a national or international stock exchange. A more detailed definition of interested parties can be obtained from the form referenced above.

44. **PROHIBITION AGAINST USED OR REFURBISHED**: Unless expressly permitted in the solicitation published by the State, Vendor must provide new, unused commodities, and is prohibited from supplying used or refurbished commodities, in fulfilling its responsibilities under this Contract.

45. **VOID CONTRACT CLAUSES** - This Contract is subject to the provisions of West Virginia Code§ SA-3-62, which automatically voids certain contract clauses that violate State law.

46. **ISRAEL BOYCOTT**: Bidder understands and agrees that, pursuant to W. Va. Code§ SA-3-63, it is prohibited from engaging in a boycott of Israel during the term of this contract.

DESIGNATED CONTACT

Vendor appoints the individual identified in this Section as the Contract Administrator and the initial point of contact for matters relating to this Contract.

(Name, Title) **Dan Hardin, Senior Vice President and General Manager**

(Printed Name and Title) **Dan Hardin, Senior Vice President and General Manager**

(Address) **45 Commerce Drive, Suite 5, Augusta, ME 04332**

(Phone Number)/ (Fax Number) **207-622-7153/ 207-623-5125**

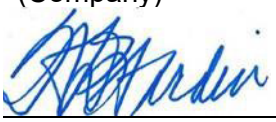
(Email address) **dhardin@changehealthcare.com**

CERTIFICATION AND SIGNATURE

By signing below, or submitting documentation through wvOASIS, I certify that: I have reviewed this Solicitation/Contract in its entirety; that I understand the requirements, terms and conditions, and other information contained herein; that this bid, offer or proposal constitutes an offer to the State that cannot be unilaterally withdrawn; that the product or service proposed meets the mandatory requirements contained in the Solicitation/Contract for that product or service, unless otherwise stated herein; that the Vendor accepts the terms and conditions contained in the Solicitation, unless otherwise stated herein; that I am submitting this bid, offer or proposal for review and consideration; that I am authorized by the vendor to execute and submit this bid, offer, or proposal, or any documents related thereto on vendor's behalf; that I am authorized to bind the vendor in a contractual relationship; and that to the best of my knowledge, the vendor has properly registered with any State agency that may require registration.

By signing below, I further certifj1that I understand this Contract is subject to the provisions of West Virginia Code§ 5A-3-62. which automatically voids certain contract clauses that violate State law: and that pursuant to W. Va. Code 5A-3-63, the entity entering into this contract is prohibited from engaging in a boycott against Israel.

Change Healthcare Pharmacy Solutions, Inc.
(Company)



(Authorized Signature) (Representative Name, Title)

Dan Hardin, Senior Vice President and General Manager 5/18/22
(Printed Name and Title of Authorized Representative) (Date)

207-622-7153/ 207-623-5125
(Phone Number) (Fax Number)

dhardin@changehealthcare.com
(Email Address)

ADDENDUM ACKNOWLEDGEMENT FORM
SOLICITATION NO.: CRFQ BMS2200000002

Instructions: Please acknowledge receipt of all addenda issued with this solicitation by completing this addendum acknowledgment form. Check the box next to each addendum received and sign below. Failure to acknowledge addenda may result in bid disqualification.

Acknowledgment: I hereby acknowledge receipt of the following addenda and have made the necessary revisions to my proposal, plans and/or specification, etc.

Addendum Numbers Received: No addendum release
(Check the box next to each addendum received)

☐ Addendum No. 1	☐ Addendum No. 6
☐ Addendum No. 2	☐ Addendum No. 7
☐ Addendum No. 3	☐ Addendum No. 8
☐ Addendum No. 4	☐ Addendum No. 9
☐ Addendum No. 5	☐ Addendum No. 10

I understand that failure to confirm the receipt of addenda may be cause for rejection of this bid. I further understand that any verbal representation made or assumed to be made during any oral discussion held between Vendor's representatives and any state personnel is not binding. Only the information issued in writing and added to the specifications by an official addendum is binding.

Change Healthcare Pharmacy Solutions, Inc.

Company

Authorized Signature

May 18, 2022

Date

NOTE: This addendum acknowledgement should be submitted with the bid to expedite document processing.

SPECIFICATIONS

1. **PURPOSE AND SCOPE**: The West Virginia Purchasing Division is soliciting bids on behalf of Bureau for Medical Services (BMS) to establish an open-end contract for Preferred Drug List (PDL), Preferred Product List (PPL), High-Cost Physician-Administered Drugs List (HCPADL), and State Maximum Allowable Cost (SMAC) services for the West Virginia Medicaid Program. The contract awarded pursuant to this RFQ will apply to both fee-for-service (FFS) and managed care organization (MCO) programs for PDL/PPL/HCP ADL/SMAC services. Currently, pharmacy benefits are provided under the FFS Program, but medical/dental services are provided both by MCOs and the FFS Program. BMS reserves the right to include the MCO populations in these services if pharmacy benefits should be provided by MCOs during the life of the contract awarded pursuant to this RFQ.

   As of January 09, 2022, there were 624,685 members enrolled in the Medicaid FFS pharmacy program. As of January 09, 2022, there were 508,135 members enrolled in the three (3) MCO's for medical/dental coverage, leaving a total of 116,550 in FFS.

   BMS is currently a member of the Sovereign States Drug Consortium (SSDC). The SSDC (https://www.rxssdc.org/) negotiates supplemental drug rebates and rebates for non-drug products. The status of drugs on the PDL is determined by considering the cost of drugs net of the rebates afforded by membership in the SSDC. BMS and/or BMS Fiscal Agent invoices and collects Federal, non-drug, and/or supplemental drug rebates.

   This solicitation may be funded in whole or in part with Federal Funds and thus this solicitation and its resulting awarded contract are subject to the requirements of Attachment 1: Federal Funds Addendum.

   NOTE: THE WEST VIRGINIA DEPARTMENT OF HEALTH AND HUMAN RESOURCES (WVDHHR) HAS DEVELOPED AN EEOP UTILIZATION REPORT AND IT IS AVAILABLE AT:

   http://www.wvdhhr.org/pdfs/Hl .5%20Utilization%20Report%20and%20EEO%20policy.pdf

2. **DEFINITIONS**: The terms listed below shall have the meanings assigned to them below. Additional definitions can be found in section 2 of the General Terms and Conditions.

   2.1 **"Contract Services"** means PDL, PPL, High-Cost Physician-Administered Drugs, and SMAC services including clinical review services, contract administration, supplemental drug and product rebate support, reporting, pharmacy newsletter, and other services required to support the BMS PDL, PPL HCPADL, and SMAC pricing for drugs and products as more fully described in these specifications.

   2.2 **"Pricing Page"** means the page, contained in wvOASIS upon which Vendor should list its proposed price for the Contract Services.

2.3 **"Solicitation"** means the official notice of an opportunity to supply the State with goods or services that is published by the Purchasing Division.

3. RESPONSE TO QUALIFICATIONS

Vendor, or Vendor's staff, if requirements are inherently limited to individuals rather than corporate entities, shall have the following minimum qualifications:

Note: Vendor shall provide documentation to indicate they have the capability to provide staff meeting these qualifications. This documentation should be included with the bid but must be provided prior to award.

3.1 A minimum of five (5) years of experience within the last ten (10) years in implementing and managing PDL and SMAC programs for a minimum of three (3) individual state Medicaid pharmacy programs. Vendor should provide documentation to support meeting this requirement with their bid but must provide the documentation prior to award. Documentation to support meeting the requirement includes, but is not limited to, listing of contracted States where this service is provided.

With more than four decades of successful Medicaid-focused experience, Change Healthcare continues to be a trusted partner and advisor to state Medicaid programs and an innovative and respected leader in the Medicaid industry. Change Healthcare has utilized its wealth of knowledge and experience to provide programs and services to its state Medicaid clients that are recognized across the nation as both innovative and effective. Expert, clinically focused staff continues to make Change Healthcare unique in this industry.

In 2015, Change Healthcare implemented the preferred drug list (PDL), preferred provide list (PPL), and State Maximum Allowable Cost (SMAC) program for BMS and continues to administer those programs today and looks forward to building on its long, collaborative partnership. Presently, Change Healthcare is partnered with sixteen states, providing a varying degree of Medicaid pharmacy benefit solutions and support services to its partners. Many of these partnerships have existed for decades, allowing great collaboration with partners to contain costs while providing superior pharmacy experiences for both the state pharmacy benefit sponsors and their Medicaid patient populations.

A chart that details how Change Healthcare exceeds the minimum requirements specified in 3.1 with regards to PDL and SMAC services by state and number of years is provided in Appendix A.

3.2 Vendor shall provide staff with experience in the administration of a PDL, PPL, and SMAC programs including:

Change Healthcare's physicians, pharmacists, and clinical analysts work together with BMS to ensure that the pharmacy benefit provided is of the highest quality possible while being fiscally prudent and mindful of the burden on providers and members. This team regularly reviews current practices in pharmacy management and always considers ways to innovate and improve available services.

Change Healthcare welcomes feedback from clients and can offer suggestions for improvement of utilization management efforts to improve quality and decrease costs

and burdens on the system. The board-certified physicians on staff all maintain part-time clinical practices, which provide them with a unique view of issues from the provider's viewpoint. This insight can be very helpful when considering the potential impact of various policy and PDL changes. Change Healthcare's team of pharmacists are also very experienced and have served in many capacities over the years and understand the issues facing pharmacy providers, both large and small, and will bring to the discussions viewpoints that are balanced and allow BMS to consider the impact of decisions on pharmacy providers as well as members and prescribers.

3.2.1 Account manager who is a registered pharmacist, actively licensed with the Board of Pharmacy for the state in which they are employed and in good standing, with a minimum of three (3) years' experience in the administration of Medicaid FFS and/or Medicaid MCO services included in 3.2.

Change Healthcare's designated Clinical Account Manager is a registered pharmacist with eight years of Medicaid experience involving an in-depth PDL knowledge base as well as P&T support and P&T Committee presentation expertise.

For the last two years, he has managed the West Virginia account in implementing and managing their PDL, PPL, and SMAC programs. His experience with SMAC extends to managing four state SMAC programs and a RetroDUR program. His experience in and knowledge of the West Virginia programs will allow him to continue supporting BMS with proactive clinical insight.

3.2.2 Clinical pharmacist who is a registered pharmacist, actively licensed with the Board of Pharmacy for the state in which they are employed and in good standing, with a minimum of three (3) years' experience in the administration of Medicaid FFS and/or Medicaid MCO services included in 3.2.

Change Healthcare has designated a clinical pharmacist who will act as the account manager and registered clinical pharmacist for BMS. He has eight years of experience in Medicaid FFS services and has worked with three states over the past two years, providing clinically appropriate and fiscally responsible recommendations for PDL placement to P&T Committees.

3.2.3 One physician with a Board Certification in infectious disease and expertise with drugs used in the treatment of Hepatitis C and HIV/AIDS and in good standing with the Board of Medicine or Board of Osteopathic Medicine in the state in which that person is licensed with a minimum of three (3) years' experience supporting the administration of Medicaid FFS or Medicaid MCO services included in 3.2.

Change Healthcare's clinical team is made up of board-certified physicians who provide a high level of clinical pharmacy support. One of Change Healthcare's physicians is board certified in Internal Medicine and Infectious Diseases. Her continued part-time practice involves the ongoing management of all infectious diseases including COVID-19, Hepatitis C, and HIV AIDS. She has worked

continuously since 2007 in supporting the administration of all aspects of Medicaid FFS and Medicaid MCO pharmacy services. This part-time clinical practice offers clients a unique view of pharmacy issues—from both the State and provider perspective. She is a member of the American College of Physicians, the Maine Medical and Maine Osteopathic Societies, and several professional Infectious Disease Societies. She received her Doctor of Osteopathy from the University of New England College of Osteopathic Medicine.

3.2.4 One physician with a Board Certification in psychiatry and expertise with drugs used to treat mental health disorders, and in good standing with the Board of Medicine or Board of Osteopathic Medicine in the state in which they are licensed with a minimum of three (3) years' experience supporting the administration of Medicaid FFS or Medicaid services included in 3.2.

Board certified in general and geriatric psychiatry, with specific expertise in clinical trial analysis, health policy, forensic and organizational psychiatry, neuropsychiatry, and psychopharmacology, Change Healthcare's Associate Medical Director has been with the organization since 2009 and is a member of the clinical team with direct experience since that time assisting with the administration of all aspects of the pharmacy services outlined in 3.2. He maintains a part-time practice of both forensic and clinical psychiatry in Portland, Maine and has extensive expertise in health care policy analysis. In addition to direct patient care, his practice provides consultation to various foundations, businesses, and families as well as government affairs involving multi-stakeholder efforts in the health care space. He remains actively involved on a daily basis with overseeing the clinical and policy aspects of the pharmacy benefit of multiple State Medicaid clients.

3.2.5 One physician with board certification in hematology and/or oncology, and in good standing with the Board of Medicine or Board of Osteopathic Medicine in the state in which that person is licensed with a minimum of three (3) years' experience in supporting administration of Medicaid FFS or Medicaid MCO services included in 3.2.

Change Healthcare's clinical team also includes a physician board-certified in Internal Medicine and Hematology. She has been in practice for more than 20 years, providing care to patients in Maine with benign and malignant hematologic conditions. She joined the Change Healthcare clinical team in 2015 and brings more than 30 years of relevant experience to the clinical team and more than six years of experience supporting the administration of Medicaid FFS and Medicaid MCO services. She currently also holds the position of Assistant Medical Director at Community Health Options, one of the original not-for-profit health insurance cooperatives born out of the ACA, which allows her to provide insights into utilization management techniques utilized in the commercial pharmacy market. She works closely with Change Healthcare's Medical Directors and clients, bringing innovative clinical expertise with her consultation to states including Iowa, Maine, Mississippi, Ohio, Pennsylvania, Vermont, and West Virginia. Her experience includes utilization management, prior authorization, PDL design and implementation, new drug evaluation, quality assurance, multidisciplinary

program development, and clinical trial implementation. Her industry knowledge combined with real-world medical experiences prove to be beneficial to Change Healthcare's Medicaid clients.

3.2.6 Rebate Manager with a minimum of three (3) years' experience in the administration of a Medicaid Federal drug rebate and supplemental drug rebate program.

BMS will continue to work with its designated Change Healthcare Rebate Manager. She has been a member of Change Healthcare's Rebate department for more than seven years, starting as a Rebate Specialist. In her current position as Manager of Medicaid Drug Rebate Negotiated Contracts, she works directly with state pharmacy directors to ensure the quality of individual state contracts. She oversees the day-to-day operations of the Supplemental Rebate contract team, negotiating additional rebates for states beyond the CMS Federal Rebate. She also supports the Sovereign States Drug Consortium (SSDC) project and is highly knowledgeable in CMS rebate guidelines. She has helped streamline processes and procedures, developing operating standards to more effectively and efficiently serve clients.

3.2.7 SMAC pricing manager with a minimum of three (3) years' experience in the administration of a Medicaid FFS SMAC pricing program.

BMS will continue to work with the current Change Healthcare designated SMAC pricing manager. She has worked with the West Virginia SMAC program for nine years, achieving millions of dollars in savings. She has been actively involved in implementing the SMAC programs in ten states and is currently responsible for maintaining and reviewing all SMAC pricing, as well as working to create the maximum cost savings possible for state clients.

4. RESPONSE TO MANDATORY REQUIREMENTS

4.1 Mandatory Contract Service Requirements and Deliverables: Contract Services must meet or exceed the mandatory requirements listed below.

4.1.1 Vendor shall provide program management and coordination by meeting on a schedule to be mutually agreed upon by all parties, as referenced in Section 4.1.4 and 4.1.5 below, or at BMS request, and providing the data files required for the management and coordination of Contract Services with BMS and/or BMS FFS fiscal agent, the Medicaid MCO vendors (if applicable), the Pharmaceutical and Therapeutics (P & T) Committee, the SSDC and its Vendor, the prior authorization Vendor, and any other business partner associated with PDL, PPL, HCPADL, and SMAC programs. The data files will be loaded in the Claims Processing System and pertinent information is to be posted on the BMS Pharmacy website.

Change Healthcare and BMS currently have a successful partnership serving the complex data interaction and communication needs between key stakeholders. This includes, but is not limited to, BMS' Medicaid Fiscal Agent, the P&T Committee, the prior authorization vendor, and other business partners to coordinate updates and changes to the PDL, PPL, and the SMAC list. The team looks forward to the opportunity to continue those relationships based on the longstanding tradition of staff members and systems collaborating and integrating with other key stakeholders to ensure the overall success of the project. Change Healthcare fully intends to continue these positive relationships going forward.

As the current and only administrator for SSDC since its inception, Change Healthcare will continue using a collaborative approach to ensure successful outcomes for BMS. Change Healthcare intends to provide the same superior level of program management and coordination of PDL, PPL and SMAC activities with BMS and all other required stakeholders that has been delivered in previous years.

4.1.2 Vendor shall comply with all federal regulations, including confidentiality of rebate related data which can be found at https://www.ssa.gov/OP Home/ssact/title19/1927.htm and the State Plan filed and approved by the Centers for Medicare and Medicaid Services (CMS) as stated in https://dhhr.wv.gov/bms/CMS/SMP/Pages/WV-State-Medicaid- Plan.aspx

Change Healthcare's drug rebate management program and staff are fully compliant and will continue to comply with all current state and federal regulations, including the State Plan (RFP Attachment B) filed and approved by CMS and the Health Insurance Portability and Accountability Act (HIPAA) provisions. Change Healthcare is aware of the confidential nature of the rebate-related data and maintains strict security standards to ensure that confidential information is kept secure.

4.1.3 Vendor shall assist BMS with writing State Plan Amendments related to the Contract Services programs.

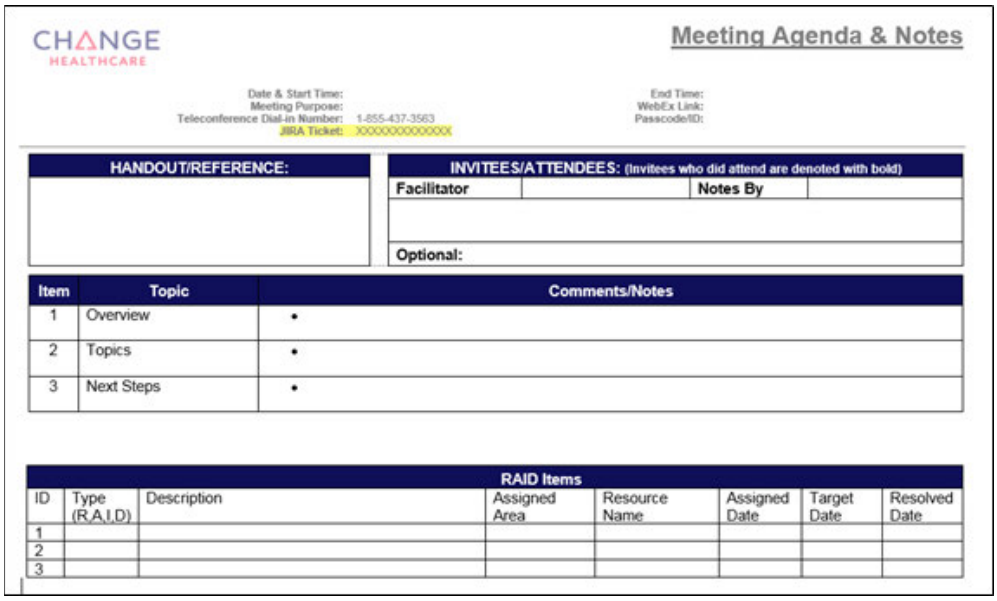
Change Healthcare has experience assisting BMS and other states in the development of their State Plan Amendments. Change Healthcare's experienced team has decades of involvement with communications and interactions with CMS including, but not limited to, the drafting and submission of State Plan Amendments. Change Healthcare's presence in multiple states, providing varying levels of pharmacy and Medicaid support, will ensure that BMS is current and in-line with other Medicaid programs.

4.1.4 Vendor shall be available for physical and/or virtual appearances, at no additional cost, before the West Virginia Legislature or other interested parties as requested by BMS at a maximum of five (5) times per calendar year.

Change Healthcare is available for physical or virtual appearances before the West Virginia Legislature as requested.

4.1.5 Vendor shall facilitate status meetings with BMS including meeting agendas and minutes. Meeting minutes must be provided to BMS within ten (10) working days of each meeting by email, including the P & T Committee meetings, which are to be held quarterly. Status meetings will be held on an agreed upon schedule, currently bi-weekly, by BMS and the Vendor via conference call.

As part of the facilitation and management of the status meetings, the Clinical Account Manager prepares and distributes the meeting agenda, prepares the status report, and any supporting documentation. Change Healthcare provides the meeting minutes, tracking of any action items that may be identified during the meeting to BMS within ten working days after the conclusion of the meeting. This is a common practice for all pharmacy clients and the team will bring best practices to the facilitation and management of the status meetings. The following figure is an example of the agenda template:



CHANGE HEALTHCARE

Meeting Agenda & Notes

Date & Start Time: End Time:
Meeting Purpose: WebEx Link:
Teleconference Dial-in Number: 1-855-437-3563 Passcode/ID:
JIRA Ticket: XXXXXXXXXXXX

HANDOUT/REFERENCE:	INVITEES/ATTENDEES: (Invitees who did attend are denoted with bold)
	Facilitator		Notes By	
	Optional:

Item	Topic	Comments/Notes
1	Overview	•
2	Topics	•
3	Next Steps	•

RAID Items

ID	Type (R,A,I,D)	Description	Assigned Area	Resource Name	Assigned Date	Target Date	Resolved Date
1							
2							
3							

Figure 1: Meeting Agenda Template Sample

4.1.6 Vendor shall provide staff to meet the needs of BMS and BMS partners to assist in managing Contract Services programs via phone, email, and face to face meetings as needed, at no additional cost.

Change Healthcare will continue the collaborative partnership with BMS where the designated Clinical Account Manager will maintain oversight for the account and will be the single point of contact between Change HealthCare's internal teams and BMS. The Clinical Account Manager will continue to be supported by the entire enterprise, ensuring an appropriate number and quality of local and corporate staff to support to meet BMS' needs and expectations. Additionally, Change Healthcare provides support from a Regional Pharmacy Director, Chief Services Officer for Account Management, Industry Relations/Rebate Specialist, Board Certified Physicians, and Senior Vice-President and General Manager, who is also a pharmacist.

Together, Change Healthcare coordinates exceptional service and supports the States served. Throughout the lifecycle of the implementation, a Project Manager will also be available as a liaison to the team to assist in the facilitation of meetings and coordination of efforts. BMS and Change Healthcare's staff of subject matter experts and leadership will meet often for status updates and discussions as needed. At the time of operational transition, Change Healthcare will have dedicated staff and management that will communicate with BMS staff frequently and have regularly scheduled meetings.

"Thank you for the support these last few days as the state worked with our sister agency to ensure care for a medically fragile foster child. Through your efforts with the PCP and specialty pharmacy, we were able to approve the patient's prior authorization for the requested number of doses to avoid future delays in care. Your patience with the volatile situation allowed the Pharmacy Unit to focus on patient care without further escalation of tensions. You provided guidance and advice that will inform the state's action with their sister agency to avoid situations from becoming similarly volatile."—Change Healthcare State employee

4.1.6.1 Vendor should submit with bid, but must submit prior to award, the names and resumes for staff assigned to this contract including, but not limited to account manager, clinical pharmacist, physicians, rebate manager, and SMAC pricing manager.

Change Healthcare proposes to continue supporting BMS with the key staff and support team that have successfully partnered with BMS to meet their needs over the past seven years. Ryan Fell, PharmD will continue to serve BMS as Clinical Account Manager. His experience and familiarities with the specific requirements of this program will provide for a seamless transition. In addition, staff supporting this contract will continue to include Drs Biczak, Barkin, and Hedlund; Rebate Manager Cherieann Harrison; SMAC Pricing Manager Christine Deprofio; Pharmacy Operations Consultant and 340B expert John Grotton. Resumes are provided in Appendix B.

4.1.6.2 Vendor shall provide an account manager that will be available during business hours of 8:00 A.M. to 5:00 P.M. Eastern Standard Time (EST), Monday through Friday, excluding West Virginia (WV) state holidays. https://personnel.wv.gov/employees/benefits/pages/holidays.aspx

This person is responsible for the overall operations of the contracted deliverables included in this contract.

The Clinical Account Manager will be available to BMS Monday through Friday from 8:00 A.M. to 5:00 P.M. Change Healthcare looks forward to continuing to provide exceptional support to BMS.

4.1.6.3 Vendor shall provide an account manager who shall attend P & T Committee and Drug Utilization Review (DUR) Board Meetings to offer advice to BMS on clinical and financial issues relating to the Contract Services. The P & T Committee and DUR Board are each scheduled to meet four (4) times annually in Charleston, WV or virtually as deemed necessary.

Change Healthcare looks forward to continuing to support and provide the BMS P&T Committee and DUR Board with the most relevant clinical and fiscal considerations regarding the PDL. The Clinical Account Manager will work with the expertise of the three board-certified physicians of the clinical team and the Industry Relations/Rebate Specialist and Rebate team to make clinical and financial recommendations.

4.1.6.4 Vendor shall provide for the services of three (3) physicians, as outlined in Sections 3.2.3, 3.2.4, and 3.2.5 of this RFQ, actively licensed with the Board of Medicine or Osteopathic Medicine for the state in which they are employed. A minimum of one (1) physician shall attend the quarterly P & T Committee meetings and DUR Board Meetings in-person or virtually to offer advice to BMS on clinical issues relating to Contract Services and a minimum of one (1) physician shall be available by telephone and/or email to BMS during business hours of 8:00 A.M. to 5:00 P.M. EST, Monday through Friday, excluding WV state holidays.

Change Healthcare is proposing the services of three physicians as required in Section 3.2.3, 3.2.4 and 3.2.5 of this RFQ.

First-class clinical services are driven by having the right combination of professionals, processes, and technology in place to make a positive impact on clinical and fiscal outcomes for BMS. Change Healthcare offers a team of clinical experts with a high level of experiences and abilities, capable of providing clinical oversight of all programmatic aspects of the pharmacy program.

Change Healthcare has been providing support to state Medicaid DUR Boards and P&T Committees for over two decades. Providing such services to multiple state Medicaid programs, the primary goal is to

provide BMS with clinically effective, value driven PDL recommendations, supporting data and analysis in a manner that is accurate, transparent, unbiased, and user-friendly. Change Healthcare's designated Clinical Account Manager and at least one of the board-certified physicians will be available to present the therapeutic class reviews (TCRs), drug monographs, financial materials, and any other relevant information to the DUR Board and P&T Committee meetings.

Additionally, BMS will continue to have access to a physician who is available Monday through Friday from 8:00 A.M. to 5:00 P.M. EST.

4.1.6.5 Vendor shall provide for the services of a rebate manager. This individual shall be available to BMS by telephone and email during business hours of 8:00 A.M. to 5:00 P.M. EST, Monday through Friday, excluding WV state holidays. This individual is responsible for, at a minimum, completion and management of rebate contracts, reporting of contract status, contract disputes, and pricing and contract files and reports for rebate invoicing.

Change Healthcare continues to provide an experienced Rebate Manager who is available Monday through Friday from 8:00 A.M. to 5:00 P.M. She will continue to provide expertise in contract management and SR/DME Pricing File as she has since 2016.

4.1.6.6 Vendor shall provide for the services of a SMAC pricing manager. This individual shall be available to BMS by telephone and email during business hours of 8:00 A.M. to 5:00 P.M. EST, Monday through Friday, excluding WV state holidays. This individual is responsible, at a minimum, for management of the SMAC program, oversight of the selection of generics, other drugs, and products to which SMAC prices will be applied, calculation and reporting of SMAC pricing as well as savings, providing documentation for price posting, and advising and resolving SMAC pricing disputes. The Vendor shall provide BMS by email with weekly pricing disputes and recommendations at a schedule to be mutually agreed upon by the Vendor and BMS.

BMS will continue to work with its designated SMAC pricing manager. She has supported BMS SMAC for seven years and understands the requirements as defined by BMS as she is responsible for maintaining and reviewing all SMAC pricing, as well as creating the greatest savings possible for State clients. She will continue to provide timely expert services which include but are not limited to providing weekly pricing disputes and recommendations. Working in concert with the Clinical Account Manager, she will continue to provide recommendations on the selection of generics, other drugs, and products to which SMAC prices will be applied, calculation and reporting of SMAC pricing as well as savings, and providing documentation for price posting.

She will be available to BMS Monday through Friday from 8:00 A.M. to 5:00 P.M. EST.

4.1.6.7 Vendor shall complete background checks http://www.gpo.gov/fdsys/pkg/FR-201l-02-02/pdf/2011-1686.pdf for current and potential employees to ensure that staff meets the minimum requirement under state and federal statute and/or regulations. See Attachment A (West Virginia Business Rules) and B (West Virginia Medicaid State Plan) for State Requirements. Vendor shall not employ persons who are excluded from Medicare or Medicaid participation by the Federal Office of the Inspector General or any state Medicaid program. The exclusion database can be found at: https://exclusions.oig.hhs.gov/.

Change Healthcare's Talent Acquisition Team conducts background checks on all prospective employees, contractors, and consultants. The scope of the background check includes employment and education verification, criminal record screening, social security trace, and professional employment reference checks. All employees are required to go through HIPAA privacy training through the Change Healthcare University web-based training tool, including the recertification of the training on an annual basis. In addition, all employees must sign confidentiality and security agreements. Depending upon the contractual obligations of the business unit for which the employee works, employees may be required to complete drug screens, as permitted by applicable law. All staff will meet the minimum requirements under state and federal statute and/or regulations. Change Healthcare is an Equal Opportunities Employer.

4.1.6.8 Changes in staff positions of account manager, clinical pharmacist, physicians, rebate manager and SMAC pricing manager shall be approved by BMS prior to the change.

In the event of changes to the Clinical Account Manager, clinical pharmacist, physicians, rebate manager, and SMAC pricing manger, Change Healthcare in conjunction with the Talent Acquisition Team will present qualified replacement personnel for BMS approval.

4.1.6.9 Vendor participation changes for any given meeting shall be approved by BMS at least five (5) working days prior to the scheduled meeting date.

Change Healthcare fully intends to provide the designated contract staff for all required meetings. However, in the event of a needed replacement, Change Healthcare will ensure that BMS approves the change at least five working days prior to the scheduled meeting date.

4.1. 6.10 If contracted positions are not readily available, the Vendor shall provide a qualified backup to address any immediate needs requested by the state at no additional charge.

Change Healthcare has a team of highly qualified pharmacists, physicians, rebate, and SMAC team members that support multiple states and accounts. In the unlikely event that a contracted position is not readily available, Change Healthcare will identify a qualified replacement to ensure that BMS can address any and all immediate needs.

4.1.7 Vendor shall agree that any and all data provided to the Vendor by BMS or BMS partners, and any and all data collected, created, summarized, and/or aggregated, deliverables submitted to BMS or BMS partners, and reports created under the contract pursuant to this RFQ, are the sole property of BMS, intended for the purposes of supporting the Medicaid and Pharmacy programs in any manner deemed appropriate by BMS. None of these materials may be used by the Vendor at any time or in any manner without express written BMS approval.

Change Healthcare agrees that any and all data provided to us by BMS, or its partners, along with documentation, or deliverables specifically created as a requirement of this RFQ will remain the sole property of BMS. Any Change Healthcare applications, systems, equipment, etc. used will remain the property of Change Healthcare.

4.1.8 Vendor shall develop and provide support for clinically sound and cost-effective recommendations to BMS and the West Virginia Medicaid P & T Committee to refine and manage the PDL and PPL.

For more than twenty years, Change Healthcare has helped Medicaid clients with the development and management of their preferred drug lists (PDLs), facilitating access to drugs chosen for effectiveness, safety, and overall clinical value to members. Through our administration of BMS' PDL, Change Healthcare's team continuously monitors numerous sources to stay abreast of changes in the pharmaceutical market, including monitoring the pipeline of new products, price changes, and regulatory and legislative changes that can impact pharmacy programs. The team of physicians and pharmacists are involved daily in Medicaid pharmacy operations, working with states and providers. The medical directors are actively engaged in patient care within their own private practices. The varying perspectives these experienced professionals bring will help Change Healthcare's staff provide BMS with a broad and deep view of the landscape and issues from both a clinical and regulatory view. Together, this team will bring best practices and innovative strategies to provide BMS with a clinically sound, value-driven pharmacy benefit.

4.1.9 Vendor shall facilitate meetings, present clinical and accurate cost information, develop, and distribute meeting materials such as, but not limited to, agendas, minutes, reports, and handouts for all P & T Committee meetings and provide ad hoc reports or other requested clinical and/or financial information for the DUR Board meetings throughout the year as approved by BMS. P&T Committee meeting materials shall be made available electronically to a minimum of seven (7) and a maximum of fifteen (15) P&T Committee members and a minimum of six (6) BMS staff members, two (2) weeks prior to the meeting.

Change Healthcare is well equipped to provide comprehensive management of BMS' P&T Committee and DUR Board meetings. Change Healthcare has staffed DUR Boards and P&T Committees for 25 years and does so currently in multiple states. Change Healthcare manages all aspects of P&T meetings, including drafting the agenda (in concert with the state pharmacy staff), meeting beforehand with members of the state pharmacy staff to plan the meeting content and review the proposals generated by Change Healthcare, compiling the documents for the meeting, presenting the data and analyses of the specified drugs, and preparing and distributing the meeting minutes.

Change Healthcare operates in a transparent and unbiased manner to provide fiscally sound and medically supportable recommendations to the committee. The goal is to provide analyses that are data-driven, combining efficacy and cost data to make recommendations for clinical criteria for use for prior authorization and recommendations for clinical interventions or initiatives and policy proposals. Change Healthcare seeks to provide Medicaid members with high-value treatment options that are on par clinically with options available to members in commercial plans and are non-discriminatory.

Change Healthcare will facilitate meetings and provide P&T Committee meeting materials electronically to P&T Committee members at least two weeks prior to the meeting.

4.1.10 Vendor shall develop and provide to a minimum of six (6) BMS staff members, Quarterly P & T Committee meeting agendas electronically for each P & T Committee meeting at a minimum of thirty-five (35) calendar days prior to meetings. Content shall be approved by BMS for release. Vendor shall also send the draft version of the PDL to BMS for review and comment with "Draft" status clearly marked thirty-five (35) calendar days prior to meeting electronically.

Change Healthcare's account management and clinical team members handle all aspects of the P&T Committee meetings, including drafting the electronic agenda, marked "Draft," at least 35 calendar days prior to meetings and submitting for BMS approval.

4.1.11 Vendor physician(s) and registered pharmacist(s) shall review therapeutic classes including new medications or indications as approved by the Food and Drug Administration (FDA) and present recommendations to the P & T Committee and BMS for appropriate revisions to the PDL in a live format to be mutually agreed upon by Vendor and BMS, currently on a quarterly basis.

The Change Healthcare team consisting of a pharmacist and physician will continue to support BMS live in a mutually agreed upon format at each P & T Committee meeting. At the meeting, these experienced team members provide a brief, focused review of each relevant therapeutic class, touching on the key clinical areas that are covered more extensively in the therapeutic class review (TCR) documents that are supplied to the state and Committee members prior to the meeting. This live review will highlight new medications and indications and

any new clinical data or guideline changes for each therapeutic class. The combination of providing the more extensive clinical review documents prior to the meeting and then highlighting the most pertinent information during the meeting has been a highly successful format. The goal of all of these endeavors is to provide the P &T Committee with evidence-based recommendations that will continue to support BMS' goal to have a clinically sound PDL which incorporates best clinical practices and yet be provided at the lowest possible net cost, while also considering not only pharmacy but overall medical expenditures. In addition to current PDL classes, Change Healthcare believes that it is in BMS' best interest that Change Healthcare not only consider the classes and drugs included in the PDL program, but also keeps a vigilant, proactive eye on drugs in the pipeline and makes recommendations for additions to the PDL classes.

Change Healthcare has a library of over 100 TCRs, built and continuously updated by its clinical staff that is available to BMS. Its process for reviewing the literature and including articles in the class reviews is methodical and unbiased. Change Healthcare will no less than annually review drugs within chosen therapeutic classes to affirm or change recommendations regarding PDL placement and supplemental rebate strategies.

4.1.12 Vendor shall provide meeting documents, including but not limited to agenda, clinical monographs, cost sheets, therapeutic drug reviews, pricing information and other pertinent information electronically to BMS and P&T Committee members fourteen (14) calendar days prior to meetings.

The Change Healthcare Clinical Account Manager will provide the meeting documents including, but not limited to, agenda, TCRs, drug monographs, financial materials, changes summary, provider notice, and any other relevant information electronically at least fourteen days prior to the P&T Committee.

4.1.13 Vendor shall provide meeting minutes electronically for all P & T Committee meetings. Meeting minutes will follow the current format as found on the BMS website, which can be found at: https://dhhr.wv.gov/bms/BMS%20Pharmacy/PharmTheraComm/Pages/P-and-T-Committee-Meetings.aspx. Minutes are due to BMS for review no later than ten (10) working days after each P & T Committee meeting.

As part of the facilitation and management of the P&T meetings, the Clinical Account Manager prepares and distributes the meeting agenda, prepares the status report, and any supporting documentation. Change Healthcare provides the meeting minutes, tracking all relevant discussions and status changes to BMS within ten business days after the conclusion of the meeting.

4.1.14 Vendor shall provide BMS and the P & T Committee with therapeutic class reviews that compare drugs and products, at a minimum, for efficacy, safety, side effects, dosing, indications, prescribing trends, and cost efficiencies of each drug or product class. These reviews will be delivered as monographs. Vendor should submit a monograph example with their quotation but must submit prior to award electronically or on paper.

The Change Healthcare clinical team understands the critical importance of thoroughly researched, evidence-based information for the state agency and its committees to utilize in performing their task of comparing drugs within a therapeutic class. This is a fast-moving, information laden area of medicine that requires dedication to the utilization of evidence-based practices in assessing the various drug therapies. Change Healthcare's clinical monographs, including TCRs, utilize a proprietary evidence-rating system. Change Healthcare is particularly mindful of comparative clinical trials and uses both externally provided and internally generated information to inform such analyses. These monographs provide detailed descriptions of clinical trials which, at a minimum, inform on efficacy, safety, adverse effects, indications, dosing, and drug-drug interactions.

The team has specific expertise in understanding the true meaning of clinical trials which can inform BMS and the P&T Committee on cost efficiencies, prescribing trends, and market projections. The Change Healthcare team translates clinical trial data into readily understandable and replicable information that informs all relevant stakeholders.

To accomplish this, the Change Healthcare clinicians review many sources of information, including full text journal articles, evidence-based clinical guidelines, prescribing information, FDA updates and the compendia, such as Micromedex®, Facts & Comparisons®, the National Comprehensive Cancer Network Guidelines and Compendia, Lexicomp®, UptoDate®, Dynamed®, The Medical Letter® and the Cochrane Library. In addition, Change Healthcare secures access to full-text articles from journals and textbooks through Reprints Desk and Clinical Key.

A sample therapeutic class review is included as Appendix D.

4.1.14.1 Vendor shall provide to BMS and the P & T Committee members concise and systematic reviews of each therapeutic drug or product class or specific drugs or products to be presented for review by BMS or P & T Committee, including monographs, pricing information, and other pertinent information, no later than fourteen (14) calendar days prior to each P & T Committee meeting electronically.

Change Healthcare creates specific TCR/drug monographs for clients based on the presentation criteria for the individual state meetings. Change Healthcare comments and level of evidence (LOE) ratings are two unique features included in the therapeutic class reviews. Its clinical team developed these proprietary elements to specifically meet the unique information requirements of state clients and their respective committees. These, as well as pricing information, will be provided to

BMS and P&T Committee no later than fourteen calendar days prior to each P&T Committee meeting.

4.1.14.2 Vendor shall designate to BMS and the P & T Committee the Vendor's recommendation as to preferred or non-preferred status for each drug or product within each class based on current clinical and cost data.

Recommendations related to Preferred Drug List (PDL) placement, PDL and prior authorization (PA) criteria and clinical edits are formulated by Change Healthcare after thorough review of clinical evidence, net cost of therapeutic options, underlying utilization patterns and the pharmaceutical market and pipeline. The overarching goal of the recommendations made by Change Healthcare is the provision of quality pharmaceutical care to Medicaid members in the most cost-effective manner possible.

Change Healthcare's Clinical Account Manager and clinical team will present the clinical and fiscal analysis and recommendations for preferred/non-preferred status of each drug. The goal of Change Healthcare's proven format and rigorous process is to present BMS and the Committee with all the information necessary to make informed PDL decisions.

4.1.14.3 Vendor shall update and keep current all therapeutic drug and product class monographs using peer reviewed referenced materials and must grade the strength of evidence used. Monographs shall be updated at least once annually.

Change Healthcare's repository of TCRs is continuously reviewed no less than annually and updated by its clinical team. On the cover page of every TCR is the last review date and the literature searched through date. Change Healthcare will provide BMS and the P&T Committee with only the most current and up-to-date materials for review.

Change Healthcare's TCRs include a proprietary evidence rating of each study used in the review that not only grades the strength of the evidence but provides information as to whether the study looked at actual clinical outcomes versus proxy outcomes (e.g., lowering of cholesterol versus lowering of mortality).

4.1.14.4 Vendor shall review new drugs, new drug formulations, or products using a schedule agreed upon by the Vendor and BMS, at a quarterly minimum.

Change Healthcare closely monitors the drug pipeline to identify new drugs, new drug formulations, or products to market. Change Healthcare's research includes following new drug submissions and ANDA dates to provide guidance for what should occur in the PDL, not only now, but in the coming year. Additionally, the Clinical Account Manager monitors the weekly drug file for new drugs as they enter the weekly NDC files. The Clinical Account Manager and the clinical team

collaborate on the development of a clinical and fiscal materials to be presented for review by BMS and the P&T Committee.

4.1.14.5 Vendor shall advise BMS, as needed, and the P & T Committee at regularly scheduled meetings, on comparative value of new drugs or drug formulations or products that fall into categories already established on the PDL, HCPADL, and PPL.

Information provided to BMS staff and P&T Committee members will include TCRs designed to facilitate a comparison of therapeutic options based on clinical evidence that is pertinent to Medicaid and related programs. This information is tailored to the specific needs of each client and their Committees for assessing the relative value of drugs for inclusion and status on their PDLs.

Clinical reviews and financial models (including utilization data) for therapeutic classes, individual drugs, and other products will be presented to BMS in the required timeframe to allow for review by BMS staff prior to each P&T Committee review. Change Healthcare clinical and financial team members will meet with BMS to review the submitted material and PDL recommendations. Input from BMS will be incorporated into the documentation prior to sending to P&T Committee members for their review in preparation for their meeting.

4.1.14.6 Vendor shall incorporate multisource drugs into the PDL, maximizing the use of the most cost-effective drugs for inclusion on the PDL.

All rebateable formulations of a drug are considered in the PDL review process. This includes multisource drugs with appropriate comparisons of available strengths and formulations. Net prices are considered as a key factor when multiple versions of the same drug are available. It is important to note that when generic drugs first enter the market, they may not be the most cost-effective option. Change Healthcare anticipates and monitors new generic entries to the market and will recommend them for preferred status when clinically and fiscally appropriate.

4.1.14.7 Vendor shall advise BMS of new drugs appearing on the weekly reference drug data file including, but not limited to, the drug name, PDL category (if applicable), its indication, the overall value of the drug and its impact to BMS pharmacy program.

Change Healthcare provides regular updates that communicates when new products are received in the NDC file and confirms that new products are incorporated in the system with appropriate configuration coverage, service authorizations, PDL status, and limitations for BMS' program.

4.1.14.8 Vendor will provide to BMS and the members of the P & T Committee SSDC-negotiated supplemental rebates and financial analysis information for each therapeutic class or specific drugs or products under review by BMS and the P & T Committee. Drug and

product rebate information shall be kept confidential as required by 42 USC 1396r-8(b)(3)(D) https://www.gpo.gov/fdsys/granule/USCODE-2008- title42/USCODE-2008-title42-chap7-subchapXIX-sec1396r- 8/content-detail.html or future update (s).

Change Healthcare is the current administrator of the SSDC and has been for more than 16 years and will continue to provide to all members of the P&T Committee and BMS staff, as appropriate, SSDC-negotiated supplemental rebates and financial analysis information for each therapeutic class or specific drug under review by the P&T Committee. Change Healthcare acknowledges that all drug rebate information must be kept confidential as required by 42 USC 1396r-8(b) (3)(D).

4.1.14.8.1 Vendor will provide financial information for the P & T Committee for each drug or therapeutic product class at least annually, and new drugs or products as they are reviewed by BMS or P & T Committee at least quarterly, in a format that contains at a minimum, drug or product class, drug or product name, brand or generic status, current PDL or PPL status, average quantity dispensed per prescription, net cost after all rebates per prescription.

Change Healthcare will comply with all the requirements outlined in Section 4.1.14.8. The Change Healthcare team will provide to all members of the P&T Committee and BMS staff, as appropriate, SSDC-negotiated supplemental rebates and financial analyses in the form of cost sheets for each therapeutic class and specific drug under review by the P&T Committee. This information will be provided for each therapeutic class at least annually and financial information on new drugs will be prepared for review by the P&T Committee at least quarterly. At a minimum, the format will include the drug class, drug name, brand/generic status, current PDL/PPL status, and utilization information, including average quantity dispensed per prescription, and net cost (after all rebates) per prescription. Recommendations will be made in all therapeutic classes for inclusion or exclusion of each drug, based upon clinical factors, net cost, past utilization, forecasted utilization and expenditures. Change Healthcare recognizes the confidentially of rebate information and will continue to be vigilant with regard to keeping this information confidential as required by 42 USC 1396r-8(b)(3)(D).

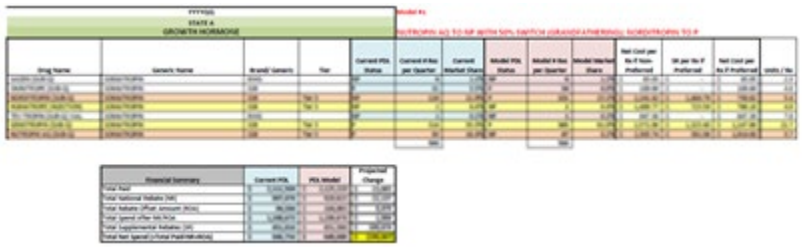


Figure 2: Sample Cost Sheet

4.1.14.8.2 Vendor shall incorporate SSDC negotiated pricing into its PDL and PPL business models, analyze SSDC pricing, and produce recommendations for a PDL and PPL using SSDC negotiated pricing on an annual basis for review of the entire PDL and any incremental pricing information as it becomes available.

As the administrator for the SSDC, Change Healthcare has access to and is knowledgeable about the details of SSDC pricing. It will incorporate SSDC-negotiated pricing into its PDL/PPL business model, pricing analyses, and all financial models provided to BMS to produce PDL and PPL recommendations. Change Healthcare will present estimated savings in a manner agreeable to BMS on at least an annual basis. Estimated savings based on recommended PDL changes are provided on the cost sheets utilized for each P&T Committee meeting. This includes estimations based on both current and projected utilization.

4.1.14.8.3 Vendor shall keep SSDC pricing information confidential and keep SSDC pricing information separate from the Vendor's other lines of business.

Change Healthcare recognizes and understands the need to keep all confidential SSDC pricing information separate from other lines of business. Change Healthcare's systems are specifically designed to keep SSDC rebate information confidential Change Healthcare agrees to maintain manufacturer price and rebate information as strictly confidential in accordance with State and Federal statutes and requirements. Change Healthcare will maintain BMS' supplemental rebate agreements/contracts separately from other clients.

4.1.14.9 Vendor shall manage BMS PDL and PPL, including but not limited to, the production of documents and data, including PDL and PPL status files needed for claims processing and PDL updates as recommended by the P & T Committee that are approved by BMS and the Secretary of the West Virginia Department of Health and Human Resources (DHHR) or PPL updates as approved by BMS.

Change Healthcare's current Clinical Account Manager and clinical team are highly experienced in the practical details of managing a complex

pharmacy benefits such as BMS'. Timely communication of documents and data including PDL and PPL status files and PDL updates is critical to this smooth operation of a constantly changing pharmacy benefit. Change Healthcare's current team is very familiar with BMS' policies and protocols and will continue to deliver documents and data on time, meeting or exceeding BMS' requirements. In addition to meeting these requirements, Change Healthcare will continue to partner with BMS to actively participate in process innovations.

4.1.14.10 Vendor must ensure that PDL and PPL are in compliance with all applicable Federal https://www.medicaid.gov/medicaid/prescription- drugs/drug-utilization-review/index.html and State https://dhhr.wv.gov/bms/BMS%20Pharmacy/DUR/Pages/Retrospective- DUR-and-Lock-In.aspx statutes and regulations and the State Plan (Attachment B,) approved by CMS.

Change Healthcare's knowledgeable, experienced clinical team will ensure that BMS PDL/PPL follows all federal and state statutes and regulations and the CMS-approved State Plan referenced in Attachment B of the RFQ.

4.1.14.11 Vendor shall prepare the PDL and PPL documents electronically in a file format that is compatible with the West Virginia Office of Technology's supported operating platform (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx to be displayed on BMS's https://dhhr.wv.gov/bms/Pages/default.aspx website for interested parties.

Change Healthcare has been successfully meeting BMS' document delivery requirements as outlined by West Virginia Office of Technology and will continue to do so.

4.1.14.12 Vendor shall comply with the standards of BMS and BMS business partners for drug and product data-file maintenance including, but not limited to, the use of therapeutic class codes, generic sequence numbers, prior authorization requirements, injectable or other dosage form indicators, replacement or change files as desired, catch-up files, or any other drug and product data file standards required by BMS and BMS business partners.

Change Healthcare will comply with the standards of BMS and BMS business partners for all drug and product data-file maintenance as it currently provides weekly and as requested by BMS.

4.1.14.13 Vendor shall comply with the requirements no later than twenty-four (24) hours after the request is made of the BMS business partners for weekly, monthly, and quarterly file deliveries.

The Change Healthcare team will ensure any requests made will be complied with within twenty-four hours.

4.1.14.14 Vendor shall establish and maintain an interface with BMS and/or BMS fiscal agent for secure document and file exchanges on no less than a weekly basis. Neither BMS and/or BMS fiscal agent will be responsible for any charges relating to this.

Change Healthcare has currently established interfaces for secure document and file exchanges with BMS and its partners. Change Healthcare will maintain these interfaces with file exchanges as required including those that require no less than a weekly update. There will be no charges to BMS or the BMS fiscal agent for these interfaces or file exchanges. BMS will continue to benefit from Change Healthcare's highly trained network services team who are responsible for establishing and maintaining data interfaces with external third parties. Change Healthcare uses state of the art technology to drive file processes, conduct file transfer quality control, support data warehouse, and development staff for code deployments and provide ongoing network support for internal staff, server, and network maintenance and monitor systems operations and up-time.

4.1.14.15 Vendor shall comply with the requirements of BMS and BMS business partners relating to the method of file exchanges, i.e., "pushing" or "pulling" data.

Change Healthcare is currently complying with the requirements of BMS and BMS business partners related to the method of file exchanges and will continue to do so. Change Healthcare systems are capable of both "pushing" and "pulling" data.

4.1.14.16 Vendor shall apply an effective date and a unique version number for each PDL, PPL, and other business documents.

Version control is a critical task when managing a complex program. Change Healthcare is experienced in providing documents with date and version control features that enable clear communication of important details.

4.1.14.17 Vendor shall ensure the quality of all files delivered to BMS and BMS business partners to provide error-free data.

Quality assurance reviews are conducted by the account management team for all weekly, monthly, and quarterly reporting activities to ensure high quality delivery.

4.1.14.18 Vendor shall update the PDL and PPL document after each P & T Committee meeting and when changes are made to the PDL and PPL as requested by BMS, no later than twenty-four (24) hours after the request is made.

Change Healthcare will continue to provide exceptional service related to the management of the PDL and PPL documents for BMS. Change Healthcare will continue to provide the updated documents after each P&T Committee meeting and no later than twenty-four hours after any additional request by BMS is made.

4.1.14.19 Vendor shall assist in development of step-care therapy and prior authorization (PA) criteria by making suggestions for step care and PA criteria to promote appropriate utilization and to enhance PDL and PPL compliance and achieve optimal savings.

Change Healthcare will continue to provide clinical and utilization management expertise by its physicians and pharmacist teams to assist BMS in creating appropriate step care and prior authorization criteria that is clinically sound, promotes compliance with the PDL/PPL, and promotes optimal cost savings for the state. Change Healthcare will continue to support the state in this regard as the incumbent and looks forward to ongoing collaboration between BMS, Change Healthcare, and the P&T Committee and DUR board.

4.1.14.20 Vendor will update the PDL and PPL document when PA criteria is changed or updated by BMS and/or the DUR Board and issue an updated version for web posting as requested by BMS and on an as needed basis, no later than one (1) business day after request is made.

Change Healthcare will continue with the current standardized process for updating the PA criteria within the PDL/PPL document as requested by BMS and/or after criteria changes by the DUR board. These updates will be made no later than one business day after the request is made.

4.1.14.21 Vendor shall provide the PDL and PPL data files no later than twenty-four (24) hours after request is made in an electronic file format as specified by BMS.

Any changes to the PDL and PPL data files by BMS will be updated within twenty-four hours after requested in the format specified by BMS.

4.1.14.22 Vendor will provide PDL and PPL data files in accordance with a schedule agreed upon by BMS and the Vendor, at a weekly minimum.

Change Healthcare will provide PDL and PPL data files at the agreed upon schedule at a minimum weekly.

4.1.14.23 Vendor shall assist BMS by providing information and responding to inquiries regarding the PDL and PPL in a mutually agreed upon timeframe.

Change Healthcare has provided and will continue to provide timely expert support and assistance to BMS in responding to any inquiries regarding the PDL and PPL in a mutually agreed upon timeframe.

4.1.14.24 Vendor will draft letters and/or make telephone calls that respond to inquiries from providers and other interested parties concerning the PDL and PPL within five (5) working days of the receipt of the inquiry.

Change Healthcare will continue to provide written or verbal responses to inquiries from providers and other parties regarding the PDL and PPL and will do so within five working days of receipt from BMS.

4.1.15 Vendor shall work with BMS and/or BMS fiscal agent and its SSDC partners to assist in drug supplemental and product rebate contract administration.

As the SSDC administrator, Change Healthcare facilitates the SR negotiation process for nearly thirteen million covered lives for the SSDC, negotiating for and securing rebates from drug manufacturers for drugs utilized. The team works with the SSDC Member States to improve the performance of their respective pharmacy programs, purchase pharmaceuticals and diabetic supplies at costs commensurate with their clinical value and understand the impact and respond appropriately to state and federal Medicaid policies and laws. As a single contractor, Change Healthcare negotiates your supplemental contracts, designs your PDL, and provides suggested prior authorization criteria **creating clinical efficiencies and streamlining the process of translating supplement rebate offers into PDL criteria**. Change Healthcare will continue working cooperatively with BMS, the SSDC partners, and the relevant stakeholders to provide SR administration in a timely manner.

4.1.15.1 All rebate agreements or contracts shall be made between BMS and manufacturers using BMS and/or CMS approved templates which will be provided by BMS. Current templates being utilized can found in the following: Special Product Rebate Agreement (Attachment D), and Supplemental Drug Rebate Agreement (Attachment E).

Change Healthcare is not a party to the rebate agreements negotiated on behalf of the SSDC Member States, and as such, all SR agreements/contracts will be made between BMS and the pharmaceutical manufacturers using the CMS approved template.

4.1.15.2 Rebate contracts must be in an electronic file format that is compatible with West Virginia Office of Technology's currently supported operating platforms (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx.

As the current administrator of the SSDC and the BMS account, Change Healthcare is expertly skilled with providing rebate contracts to BMS in the acceptable electronic file format. Change Healthcare will continue to comply with the standards set forth by this requirement.

4.1.15.3 Vendor shall work with SSDC partners to accurately determine supplemental drug or product rebate contract data.

As a long-standing member state of the SSDC, BMS has seen the benefits of this partnership. Change Healthcare will continue to work collaboratively with all SSDC partners to determine the most clinical efficient and cost-effective supplemental rebates. All data exchanges have quality control processes in place to ensure their accuracy.

4.1.15.4 Vendor shall produce and facilitate the signing of supplemental drug rebate or product rebate contracts with manufacturers, BMS, and the WVDHHR within the quarter that the rebate offer is accepted.

Change Healthcare's rebate team has a comprehensive process in place for facilitating the SR contract completion with the multiple stakeholders involved. There will be a resource available to provide updates on the status of contracts should BMS request it. Change Healthcare will ensure all contracts are signed withing the quarter the rebate offer is accepted.

The following is an example of Change Healthcare's contract status report.

[State] CY2016 Contract Status Report
[Date]

[State] YYYY Supplemental Rebate AGREEMENTS/AMENDMENTS	TOTAL	Not returned from mfg	Not returned from State	NOTES
20YY Agreements	[#]	[#]	[#]	
20YY Amendments	[#]	[#]	[#]	
TOTAL 20YY CONTRACTS/AMENDMENTS	[#]	[#]	[#]	

Current Status of [STATE] 20YY Supplemental Rebate Agreements
[#] Fully Executed 20YY Contracts
[#] SRA Sent to Mnfr.

MANUFACTURER NAME	TYPE	DATE SENT TO MNFR.	RC'D FROM MNFR.	DATE SENT TO STATE	FULLY EXECUTED	NOTES	NDCs

Figure 3: Sample SR Contract Status Report

4.1.15.5 Vendor shall be responsible for oversight and tracking of all contracts and documents at all points from origin to completion.

Change Healthcare has developed an internal web-based tool for tracking SR contracts from origin to completion. Tracking begins as soon as the contracts/ amendments are drafted and continues until fully executed. Additionally, with the continued use of Adobe Sign, Change Healthcare can now monitor the signature process with both States and manufacturers in real time.

4.1.15.6 Vendor shall assume administration of existing supplemental drug and product rebate agreements.

Change Healthcare currently manages the administration of SR agreements for BMS and will continue to do so in the accurate, efficient manner BMS has come to expect.

4.1.15.7 Vendor shall maintain BMS supplemental drug or product rebate agreements and/or contracts separately from its other clients, ensuring strict confidentiality and controls that meet Federal Requirements, which can be found at: https://www.ssa.gov/OP Home/ssact/titlel9/1927.htm

Change Healthcare maintains manufacturer price and rebate information as strictly confidential in accordance with state and federal statutes and requirements. Change Healthcare will continue to maintain BMS' SR documents separately from other clients.

4.1.15.8 Vendor shall ensure that both BMS and manufacturers receive original and/or electronically signed agreements or contracts.

Change Healthcare's detailed SR contracting process ensures both BMS and manufacturers receive electronically signed contracts/agreements upon final signature of the document. Change Healthcare retains a copy of the contract to assist the State with any ongoing service requirements.

4.1.15.9 Vendor shall provide electronic files in both Excel-compatible or equal (.xls) and text (.txt) as specified by BMS containing calculated drug supplemental unit rebate amounts (SURA) and non-drug unit rebate amounts (NDURA), along with additional specified information to BMS and/or BMS fiscal agent. See current Supplement Rate File Data Field information (Attachment C). Any cost related to the data exchange will not be incurred by BMS and/or BMS fiscal agent.

Change Healthcare's quarterly pricing files contain all Supplemental and CMS pricing information BMS will need to generate accurate invoices. Change Healthcare will work with BMS to ensure the Quarterly Pricing file formats are in the layout that is suitable to match the BMS/BMS fiscal agent predetermined file format and fields. Change Healthcare's current pricing file meets the requirements as laid out in Attachment C.

4.1.15.10 Vendor shall provide SURA and NDURA files, and contract files, and any other requested documents, to BMS and/or BMS fiscal agent within fifty (50) calendar days of the end of a quarter, in an electronic file format that is compatible with the West Virginia Office of Technology's currently supported operating platforms (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx. Reports with the following information shall accompany these files and be due within the same timeframe. Vendor shall provide report

data, including but not limited to, current and prior quarter adjustment data; historical data; and contract and contract amendment data necessary for BMS to invoice manufacturers on a quarterly basis for supplemental drug rebates and product rebates in a file format that is compatible with West Virginia Office of Technology's currently supported operating platforms (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx.

Change Healthcare agrees to provide a BMS compatible quarterly electronic file containing the calculated supplemental unit rebate amounts (SURA) and non-drug unit rebate amounts (NDURA) within 50 calendar days of the end of a quarter.

4.1.15.11 Vendor must coordinate quarterly supplemental drug rebate and product rebate submissions with submission of traditional federal drug rebates.

Change Healthcare will continue to coordinate the submission of BMS quarterly supplemental rebate pricing files and non-drug unit rebate amounts (NDURA), along with additional specified information to BMS and its Fiscal Agent.

Pricing files are built upon receipt of CMS rate files and will be provided to BMS within 50 calendar days of the end of the quarter. Change Healthcare staff are committed to providing BMS with the highest level of customer service and quality files to support accurate SRUA/NDURA invoicing.

4.1.15.12 Vendor shall provide quarterly documentation to BMS and/or its designee to support supplemental drug rebate and product rebate invoicing at National Drug Code (NDC) level in an electronic file format that is compatible with West Virginia Office of Technology's currently supported operating platforms (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx.

Change Healthcare adheres to high documentation standards and best practices in all areas of business. The rebate department is familiar with supporting state rebate invoicing and will provide any necessary documentation to BMS and/or its designee for invoicing at the NDC level. All files will be compatible with the WV Office of Technology’s currently supported version of Microsoft Office Suite.

4.1.15.13 Vendor shall ensure the accuracy of all rebate files delivered to BMS and BMS business partners. If any corrections are requested after the files are sent, the Vendor must send a corrected file within one (1) working day of request.

All Change Healthcare Rebate files go through a rigorous quality assurance process to ensure accuracy. If adjustments are identified after delivery to BMS, Change Healthcare agrees to provide corrections to the

file within one working day. Change Healthcare always aims to deliver its products on time and with precision.

4.1.15.14 Vendor shall assist BMS and/or its designee in dispute resolution activities with manufacturers as they pertain to supplemental drug rebate or product rebate calculations and contracts.

Change Healthcare negotiation staff works diligently to minimize the occurrence of disputes related to supplemental rebates. The team will communicate with providers on disputed contract related matters upon receipt notification from BMS, or their designated partner. Change Healthcare's experienced contract team will assist BMS and/or its designee in dispute resolution activities that pertain to supplemental rebate calculations, negotiated rates, PDL conditions, contract dates, and contract status designation.

Communications with providers include requesting supporting documentation, provider education, availability for follow-up questions or directions, and documenting and tracking the resolution discussion through completion. Change Healthcare agrees to maintain documentation of communication with providers, and to compile reports to present for BMS.

4.1.15.15 Vendor shall communicate with manufacturers to resolve disputes arising from supplemental drug rebate or product rebate calculations or contract issues within five (5) working days of receipt of the dispute.

Change Healthcare will reach out directly to Manufacturers within five working days of the receipt of a dispute. Designated staff will work collaboratively with manufacturers to understand dispute origin for supplemental or product disputes related to rebate calculations or contract issues.

4.1.15.16 Vendor shall communicate directly with manufacturers regarding unpaid supplemental drug rebates or product rebates upon request by BMS.

With over 40 years' experience in the Medicaid industry, Change Healthcare has established close working relationships with manufacturers. Change Healthcare will communicate directly with manufactures regarding unpaid supplemental rebates upon request by BMS. Non- payment of invoiced SR amounts is treated very seriously and is rapidly elevated until a satisfactory resolution is reached.

4.1.15.17 Vendor shall communicate the resolution of disputes in a written document to BMS within one (1) working day of resolution.

Change Healthcare will work diligently to resolve contract related disputes timely and communicate the resolution of all disputes, in writing, to BMS within one business day of the resolution.

4.1.16. Vendor shall assume administration of the current SMAC program as defined in section 4.1.16.1 through 4.1.16.12.4.

Change Healthcare is prepared to continue administrative functionality for BMS as it relates to the requirements defined. Change Healthcare uses its extensive experience in SMAC and FUL program management to partner with multiple states to develop processes to meet individual needs.

4.1.16.1 Vendor shall create, refine, and maintain the SMAC program for multiple source drug products or other drug products such as specialty drugs, and non-drug products tailored to the marketplace in West Virginia.

Changes in pharmaceutical prices and product availability occur regularly. Change Healthcare receives and reviews industry data and information provided by pharmacies to assess the SMAC program and ensure rates reflect current pharmaceutical market conditions. Constant shifts in the pharmaceutical arena may affect the price and/or availability of drug products; adjustments to the SMAC program are made periodically as needed in response to market conditions.

The team also performs comprehensive updates of the SMAC rate schedules on a regular basis and performs the reviews and analyses to set SMAC rates. Once complete, Change Healthcare seeks approval from BMS to post the SMAC rates and deliver them to the pharmacy POS for implementation. If state wholesale acquisition cost (SWAC) data are unavailable, then a combination of store surveys seeking acquisition cost data and/or analyses of WAC (or AAC) data are pursued as alternative SMAC pricing strategies for BMS to consider.

4.1.16.2 Vendor shall submit the SMAC data in a file format that is compatible with West Virginia Office of Technology's currently supported operating platforms (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx.

Change Healthcare will continue to meet with a BMS and specified teams to identify data elements and business rules specific to the SMAC interface. This will include a discussion on the type of data that needs to be exchanged, as well as an agreed-upon file format.

4.1.16.3 Vendor agrees to comply with BMS business rules, as seen in West Virginia Business Rules (Attachment A,) relating to file formats (i.e., NDC level data), schedules of delivery, type of files (i.e., change only, full files) for the SMAC program.

Change Healthcare currently complies with BMS business rules as outlined in Attachment A and will continue to do so. 4.1.16.4 Vendor shall ensure the accuracy of all SMAC files delivered to BMS and BMS business partners.

Change Healthcare will continue its streamlined and efficient verification process prior to sending the file for implementation.

4.1.16.5 Vendor shall provide SMAC lists for public viewing on BMS website and maintain archived versions that are available to BMS upon request within twenty-four (24) hours of request. The format for these files can be found on the BMS website https://dhhr.wv.gov/bms/Pages/Search.aspx?q=smac%20list

Change Healthcare will continue to provide BMS with the SMAC list for public viewing. All versions of the SMAC listed are archived and are available within 24 hours upon request by BMS.

4.1.16.6 Vendor shall ensure that each SMAC list submitted has an effective date and a unique version number.

As your longtime partner, Change Healthcare will continue to send each SMAC list with an effective date and a unique version number.

4.1.16.7 Vendor shall update the SMAC list no less than weekly, and as SMAC changes are approved by BMS.

Change Healthcare will continue to supply timely, accurate weekly updates to the SMAC file as approved by BMS.

4.1.16.8 Vendor shall coordinate activities with BMS and/or BMS fiscal agent to support the implementation and updates of the SMAC list.

Change Healthcare will continue to coordinate activities with BMS and any other parties towards implementation and updating the SMAC lists provided weekly.

4.1.16.9 Vendor shall actively pursue opportunities for expansion of the SMAC pricing list and regularly report the Vendor's SMAC activities in a schedule to be determined by BMS, at a minimum of monthly.

Change Healthcare offers a variety of services that can assist in managing utilization, controlling costs, and ensuring a SMAC program that is as equitable as possible. BMS may want to consider expanding the SMAC listing. Change Healthcare will work closely with BMS to determine the feasibility and potential savings of adding additional drugs.

4.1.16.10 Vendor shall collect acquisition cost data and other source information to support SMAC pricing.

Change Healthcare obtains and reviews industry data and information provided by pharmacies to assess the SMAC program and to ensure that rates reflect current pharmaceutical market conditions. Change Healthcare performs comprehensive updates of the SMAC rate schedules on a regularly basis and performs reviews and analyses to set SMAC rates. Once complete, Change Healthcare seeks approval from BMS to post the SMAC rates and deliver them to the pharmacy POS for implementation. If state wholesale acquisition cost (SWAC) data are unavailable, then a combination of store surveys seeking acquisition cost

data and/or analyses of WAC (or AAC) data are pursued as alternative SMAC pricing strategies for BMS to consider.

4.1.16.11 Vendor shall coordinate the addition of drugs for SMAC pricing, based on availability of generic drugs, with drugs in the same therapeutic category on the PDL and PPL to ensure that the PDL, PPL and SMAC activities result in the most cost-effective results.

Change Healthcare continuously monitors the market for price increases/ decreases/drug shortages, manages MAC disputes weekly, and conducts weekly drug file reviews so as soon as a new generic becomes available, Change Healthcare obtains acquisition data within the first few weeks it is on the market. Additionally, all MAC prices are reviewed and rebased monthly.

4.1.16.12 Vendor shall provide outreach services to the WV Medicaid providers regarding Medicaid pharmacy pricing issues and the SMAC program.

BMS' website provides contact information for providers to reach the SMAC team via dedicated phone line, fax, or email regarding Medicaid pharmacy pricing issues and the SMAC program.

4.1.16.12.1 Vendor shall establish and staff a toll-free telephone line and email address to be responsible for logging and responding to inquiries from providers regarding pricing issues. The toll-free telephone line must be available, at a minimum, of 8:00 A.M. to 5:00 P.M. EST, Monday through Friday. Vendor shall be the primary contact for all drug and product pricing inquiries.

Change Healthcare has an established and dedicated toll-free phone line specific to BMS, drawing on best practices to meet BMS' expectations for customer service. Currently, providers can call 24/7 to leave messages when calling outside of the 8:00 A.M. to 5:00 P.M. business hours, and the SMAC team will call back the next business day. The help desk is specific to SMAC reimbursement issues or questions. Questions pertaining to policy or plan information can be will be directed to Change Healthcare's main toll-free number.

Some of the services provided include the following:

- Help Desk / Support Staff
- Staff toll-free help line
- Respond to calls from pharmacists and technicians regarding MAC-specific issues and questions
- Reviews and supports reporting and analysis of SMAC reimbursement inquiries

- Provide support for dealing with all aspects of customer service such as pricing disputes, requests for information, etc.

4.1.16.12.2 The Vendor shall answer, log, and respond to telephone calls and/or other communicated messages from pharmacy providers and resolve disputes related to pricing.

Change Healthcare has developed a help desk call log application that facilitates the tracking of telephone inquiries and provides recordkeeping and performance reporting for the call center during ongoing operations. This application is a secure, web-based system with intelligent integration of core data to support efficient workflow management for call management, issue resolution, and performance reporting. Disputes are recorded, researched, and resolved in consultation with BMS.

4.1.16.12.3 Responses to providers acknowledging disputes must occur within one (1) working day of receipt.

Change Healthcare will acknowledge receipt of disputes within one working day of receipt.

4.1.16.12.4 Resolution of pricing disputes must be submitted to BMS and reported to the inquiring provider within ten (10) working days of the date of the complaint.

Resolution of pricing disputes are submitted and resolved within ten working days after receiving the SMAC review request.

4.1.17. Vendor shall assist BMS in managing a list of High-Cost Physician-Administered Drugs exempted from MCO capitation.

4.1.17.1 This list shall include drugs selected by BMS according to, but not limited to, the following criteria:

4.1.17.1.1 Must be approved by the Federal Drug Administration (FDA) with orphan status.

4.1.17.1.2 Must exceed a Wholesale Acquisition Cost (WAC) of $350,000.00 per member, annualized.

4.1.17.2 Vendor shall assist in the formulation of HCPADL drug utilization criteria as required by BMS. Vendor may be requested to provide a summary of the drug, its indication, and any therapeutic management considerations.

Change Healthcare recognizes the complexities involved with managing high-cost medications with orphan drug status. Change Healthcare will utilize the collective clinical knowledge and industry experience of its physicians, pharmacists, and other related staff to assist BMS in managing the High-Cost Physician Administered Drug List (HCPADL). Change Healthcare will continue to support and make recommendations to BMS for the establishment of clinically appropriate therapeutic management criteria in relation to the HCPADL.

4.1.18 Vendor shall provide a suite of reports for BMS which reflects the components necessary to manage the PDL, HCPADL, PPL, and SMAC programs and to support the supplemental drug and product rebate invoicing. All reports must be formatted for printing.

4.1.18.1 Vendor shall develop standard reports requested by BMS. Reports requested through this contract shall include but not be limited to, those listed below. For purposes of cost estimation, Vendors may assume a maximum of forty (40) standard reports. All reports shall be in an electronic file format that is compatible with West Virginia Office of Technology's currently supported operating platforms (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx.

4.1.18.2 Vendor shall work with BMS to develop standard reports including initial release notes with calculation methodologies and when appropriate.

4.1.18.3 Vendor shall deliver standard reports monthly on the fifteenth of the month or as requested by BMS within ten (10) working days of the request.

Change Healthcare has been able to provide BMS with an expansive suite of reports, as outlined above that are instrumental in managing the PDL, HCPADL, PPL, and SMAC programs. Change Healthcare will continue to work with BMS to standardize and format these reports as required to meet your needs. Change will continue to provide the scheduled reports on the 15th of the month or within ten working days of request.

4.1.19 Vendor shall provide report analyses to BMS that will assist BMS in making program adjustments to improve the cost efficiency of the pharmacy program. Vendor shall host regularly scheduled meetings by conference call in order to discuss reports provided by the Vendor. These meetings will be held at a quarterly minimum.

Change Healthcare utilizes reporting across multiple Medicaid states to ensure decisions and recommendations made to the states are supported by data driven analytics. Change Healthcare will continuously review these reports to identify and recommend areas of potential cost efficiency and will report these findings to BMS quarterly while working collaboratively with the account management, SMAC, and rebate teams.

4.1.20 Vendor shall submit standard reports per the terms of the contract when requested by BMS.

Change Healthcare will continue to submit the standard reports as outlined in the RFQ sections 4.1.20.1 through 4.1.20.36 per the terms of the contract when requested by BMS. Change Healthcare agrees to supply BMS with required reports monthly, quarterly, and annually and ad hoc as requested. Cost for additional services has been included in the pricing page per the RFQ.

4.1.20.1 **Reports shall include, but not be limited to: Monthly, Quarterly, and Annual Pharmacy Utilization for PDL and PPL and/or All Drugs Categories: Based on a rolling twenty-four (24) months of pre-rebate expenditures in graph or chart format, shall be delivered electronically monthly, quarterly, and annually, based on report:**

4.1.20.2 **Average dollars paid amount per member user;**

4.1.20.3 **Total dollars paid;**

4.1.20.4 **Total dollars paid by brand and by generic;**

4.1.20.5 **Average generic drug prescription cost;**

4.1.20.6 **Average brand drug prescription cost;**

4.1.20.7 **Percent of generic drugs by number of prescriptions;**

4.1.20.8 **Average paid amount per prescription.**

4.1.20.9 **Summary Monthly, Quarterly, and Annual Reports to be delivered electronically, monthly, quarterly, and annually, based on report.**

4.1.20.10 **Monthly and State Fiscal Year Statistics - Compares the current month to the same month for the previous year. Summarizes the calendar year-to- date for the current month and previous calendar year-to-date; shall contain the total amount paid, number of users, total number of prescriptions, average prescriptions per member user, average cost per prescription; number of generic prescriptions, percentage of generic prescriptions paid compared to the overall amount paid for all prescriptions, total amount paid for generic prescriptions, average generic prescription cost, average days' supply for generic prescriptions, number of brand prescriptions, percentage of brand prescriptions paid compared to the overall amount paid for all prescriptions, total amount paid for brand prescriptions, average brand prescription cost, average days' supply for brand prescriptions. At a minimum, this report shall be delivered monthly, by the fifteenth of the month.**

4.1.20.11 **Top Twenty (20) Drugs by Dollars - Lists the drug description, ranking based on amount paid, comparison from the previous year for the same period, and the percentage change from the previous year period, the percent of the overall pharmacy expenditures for the period and the percent of the overall pharmacy expenditures for the previous year period. At a minimum, this report shall be delivered quarterly on the last day of the last month in the quarter and annually, by the last day in the calendar year.**

4.1.20.12 **Top Twenty (20) Therapeutic Classes by Utilization - Lists the therapeutic class description, ranking based on number of**

prescriptions, comparison from the previous year of the same period, and the percentage change from the previous year period, the percent of the overall number of prescriptions for the period and the percent of the overall number of prescriptions for the previous year period. At a minimum, this report shall be delivered quarterly by the last day of the last month in the quarter and annually, by the last day in the calendar year.

4.1.20.13 **Top Twenty (20) Drugs by Utilization - Lists the drug descriptions, ranking based on number of prescriptions, comparison from the previous year for the same period, and the percentage change from the previous year period, the percent of the overall number of prescriptions for the period and the percent of the overall number of prescriptions for the previous year period. At a minimum, this report shall be delivered quarterly by the last day of the last month in the quarter and annually, by the last day in the calendar year.**

4.1.20.14 **Top Twenty (20) Prescribing Providers - Report including data for both numbers of prescriptions prescribed and by amount paid for prescriptions prescribed: the prescriber National Provider Identifier (NPI), prescriber name, total amount of prescription costs for prescribed drugs, total number of paid prescriptions prescribed, number of members for which prescriptions were prescribed, average price of paid prescriptions prescribed. At a minimum, this report shall be delivered quarterly, by the last day of the last month in the quarter and annually, by the last day in the calendar year.**

4.1.20.15 **Market share Summary Report - Lists the PDL and PPL therapeutic classes individually and unmanaged products collectively. This report shall provide the number of prescriptions for managed drugs and products within a therapeutic class, market share percentage for managed drugs and products within a therapeutic class, number of prescriptions for unmanaged drugs and products within a therapeutic class, and market share percentage for unmanaged drugs and products within a therapeutic class. At a minimum, this report must be provided quarterly by the last day of the last month in the quarter.**

4.1.20.16 **Therapeutic Class Market Share Report - This report shall display within each therapeutic class, the drug or product name, brand, or generic status, PDL or PPL status, number of dispensed, number of paid prescriptions for the period, percentage of prescription market share within the therapeutic class, average units per prescription, pre-rebate paid amount, and average expenditures per prescription. At a minimum, this report must be provided quarterly, by the last day of the last month in the quarter.**

4.1.20.17 **Generic Compliance Report - This report will show the total number of prescriptions of brand versus generic drugs for a specific timeframe. This report shall display the PDL managed therapeutic classes and report the number of prescriptions, number of units paid, total paid amount, generic percentage for the therapeutic class, and the generic percentage for the previous quarter. In addition, this report shall report the overall generic percentage of managed and unmanaged products. At a minimum, this report shall be provided quarterly, by the last day of the last month in the quarter.**

4.1.20.18 **PDL and PPL Compliance Report - This report will show the percent compliance with the PDL and PPL. It shall display the PDL and PPL managed therapeutic classes and report the number of prescriptions, number of units paid, total paid amount, percentage of preferred products paid for the therapeutic class, and the percentage of preferred products paid for the previous quarter. In addition, this report shall report the overall preferred percentage of managed and unmanaged products collectively. At a minimum, this report must be provided quarterly, by the last day of the last month in the quarter.**

4.1.20.19 **Weekly NDC Update Report - This report will summarize new additions to the drug reference file. At a minimum, this report shall display the PDL or PPL category, drug or product name, generic name, NDC or product code, date of FDA approval, date of database entry, and comments. This report shall be provided weekly, by close of business Wednesday.**

4.1.20.20 **Rebate Dispute Status Report - The Vendor will submit a written report detailing the status of any disputes BMS has requested the Vendor to assist in resolving. At a minimum, this report shall be provided monthly, by the fifteenth of the subsequent month.**

4.1.20.21 **SMAC Savings Report - This report shall document savings generated from the SMAC pricing program. At a minimum, this report must be provided quarterly, by the last day of the last month in the quarter.**

4.1.20.22 **PDL and PPL Savings Report - This report shall document savings generated from the PDL and PPL. At a minimum, this report must be provided quarterly, by the last day of the last month in the quarter.**

4.1.20.23 **SMAC Savings Beyond Aggregate Federal Upper Limit (FUL) Cap - This report will document assurances that multisource drug pricing is in compliance with federal regulations**

https://www.ssa.gov/OP Home/comp2/B-CFR-42.html#ft13 (See Section 447.512). At a minimum, this report shall be

provided quarterly, by the last day of the last month in the quarter.

4.1.20.24 **WV Provider Pricing Support and SMAC Dispute Resolution Report - This report shall log all pricing issues from providers and resolutions reached. This report must detail the dispute and log both approved and resolved issues during the state fiscal year, July 1-June 30, as well as open disputes still being considered. This report shall include, but not be limited to product name, NDC, prescription number, inquiry date, date of service, National Average Drug Acquisition Cost (NADAC), Wholesale Acquisition Cost (WAC), FUL, SMAC, provider acquisition cost, dispensing fee, quantity, reviewer identifier, date of outcome returned, recommendation, final outcome, comments, new SMAC, effective date, provider name, and removal of FUL effective date. At a minimum, this report must be provided weekly, by close of business Wednesday.**

4.1.20.25 **New GSN SMAC Report - Vendor shall provide a report of new products for which a SMAC is recommended. This report shall include, but not be limited to, the Generic Sequence Number (GSN), product name, SMAC, effective date, and comments. This report shall be delivered weekly, by close of business Wednesday.**

4.1.20.26 **PDL and PPL Changes Report - This report will highlight changes to the PDL and /or PPL approved by the P & T Committee and/or BMS and must be provided no later than fourteen (14) calendar days after each P & T Committee meeting.**

4.1.20.27 **Supplemental Drug Rebate Contract and Product Rebate Contract Tracking Report - This report will track all supplemental drug rebate and product rebate contracts between BMS and manufacturers in the process of being finalized. This report must include the status of each contract at all points toward completion. The report shall contain, at a minimum: labeler identifier, manufacturer name, labeler number, date contract mailed, date returned form the manufacturer, date sent to state, date sent to manufacturer, contract term, contract end date, contract year. This report shall be provided monthly by the fifteenth of the month and more often if requested, and no later than seventy-two (72) hours after request.**

4.1.20.28 **Supplemental Drug and Product Rebate Contract Details Report - This report will document all contracts finalized between BMS and manufacturers, and must include contract details such as, but not limited to: product description, NDC, labeler, contracted guaranteed net price (GNP) or contracted**

percent of price and contract type. This report shall be provided monthly, by the fifteenth of the month.

4.1.20.29 **Supplemental Drug Rebate and Product Rebate Pricing Files Quality Assurance Checklists - These reports will track the steps that are taken by the Vendor to ensure that supplemental drug rebate and product rebate pricing files are correct and accurately contain contract data. These reports must be provided within fifty (50) calendar days of the end of the quarter.**

4.1.20.30 **Supplemental Drug Rebate and Product Rebate Contract Files Quality Assurance Checklists - These reports will track the steps that are taken by the Vendor to ensure that supplemental drug rebate and product rebate contract files are correct and accurately contain contract data. These reports must be provided within fifty (50) calendar days of the end of the quarter.**

4.1.20.31 **Supplemental Drug Rebate and Product Rebate Pricing Files - Additions and Corrections Reports: These reports will track adjustments that are included on the supplemental drug rebate and product rebate pricing files and the reasons for the adjustments. These reports must be provided within fifty (50) calendar days of the end of the quarter.**

4.1.20.32 **Supplemental Drug Rebate and Product Rebate Contract Files- Additions and Corrections Reports - These reports will track adjustments that are on the supplemental drug rebate and product rebate contract files and the reasons for the adjustments. These reports must be provided within fifty (50) calendar days of the end of the quarter.**

4.1.20.33 **Supplemental Drug Rebate and Product Rebate Pricing Files Spreadsheets - These reports will contain all the data for each NDC included on the supplemental drug rebate and product rebate pricing files, along with any other pertinent rebate contract or pricing information. These reports must be provided within fifty (50) calendar days of the end of the quarter.**

4.1.20.34 **Supplemental Drug Rebate and Product Rebate Contract Files Spreadsheets - These reports will contain all the data for each NDC included on the supplemental drug rebate and product rebate contract files, along with any other pertinent rebate contract information. These reports must be provided within fifty (50) calendar days of the end of the quarter.**

4.1.20.35 **NDC Conversion Factor Report - This report will track the drugs and products that require a unit of measure conversion factor in the rate calculation. These reports must be provided within fifty (50) calendar days of the end of the quarter.**

4.1.20.36 Ad Hoc Reports - Vendor shall provide, at no additional cost to BMS, responses to ad hoc reporting requests by BMS within five (5) working days of the request throughout the duration of the contract. For cost estimation purposes, assume twenty-five (25) ad hoc reports per year. Ad hoc reports shall include the report methodology and parameters used in developing the reports.

4.1.20.37 Business Rules Document - Within two (2) months of contract award, Vendor shall provide a document that details all business rules that apply to the PDL, PPL, HCPADL and SMAC programs, as well as to the supplemental drug and product rebate invoicing, in an electronic format. This document shall contain at a minimum: processes, standard operational procedures, details regarding data file layouts, delivery schedules and maintenance of reports, management of NDCs, prior authorization requirements, contracting deliverables, pricing methodologies, telephone line processes, and all details of other business rules and procedures.

Change Healthcare has maintained a business rules document for BMS that complies with the above standards since the inception of the contract between BMS and Change Healthcare. Change Healthcare will continue to update and maintain the business rules document as needed. Business rules are tracked and dated with notation of which BMS personnel approved the change.

4.1.21 Vendor shall create data files to be shared with BMS and BMS partners relating to the PDL, PPL, HCPADL and SMAC programs.

Change Healthcare will continue to create and provide data files for BMS and BMS partners in relation to the PDL, PPL, HCPADL, and SMAC programs.

4.1.22 Vendor shall, at a minimum, create and distribute to BMS or BMS designee the following data files in an electronic format that are compatible with West Virginia Office of Technology's currently supported operating platforms (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx. Weekly files are due by close of business on Wednesdays. Quarterly files are due by last day of the last month in the quarter. As needed files are due within seventy-two (72) hours of request. Quarterly files and reports for support of rebate invoicing will be due within fifty (50) calendar days past the end of the quarter.

4.1.22.1 Weekly SMAC update file

4.1.22.2 Weekly SMAC web list for posting on BMS website, which can be found at: https://dhhr.wv.1wv/bms/BMS%20Phannacy/SMAC/Pages/default.aspx-

4.1.22.3 Weekly PDL/PPL/SMAC files. These files shall contain all available NDCs regardless of their rebate status;

4.1.22.4 Quarterly supplemental rebate rate and contract files; See Attachment C;

4.1.22.5 PDL and PPL reconciliation files when needed;

4.1.22.6 Complete PDL and PPL files when needed;

4.1.22.7 PDL and PPL file updates or complete files to be delivered to BMS, or BMS designees as needed;

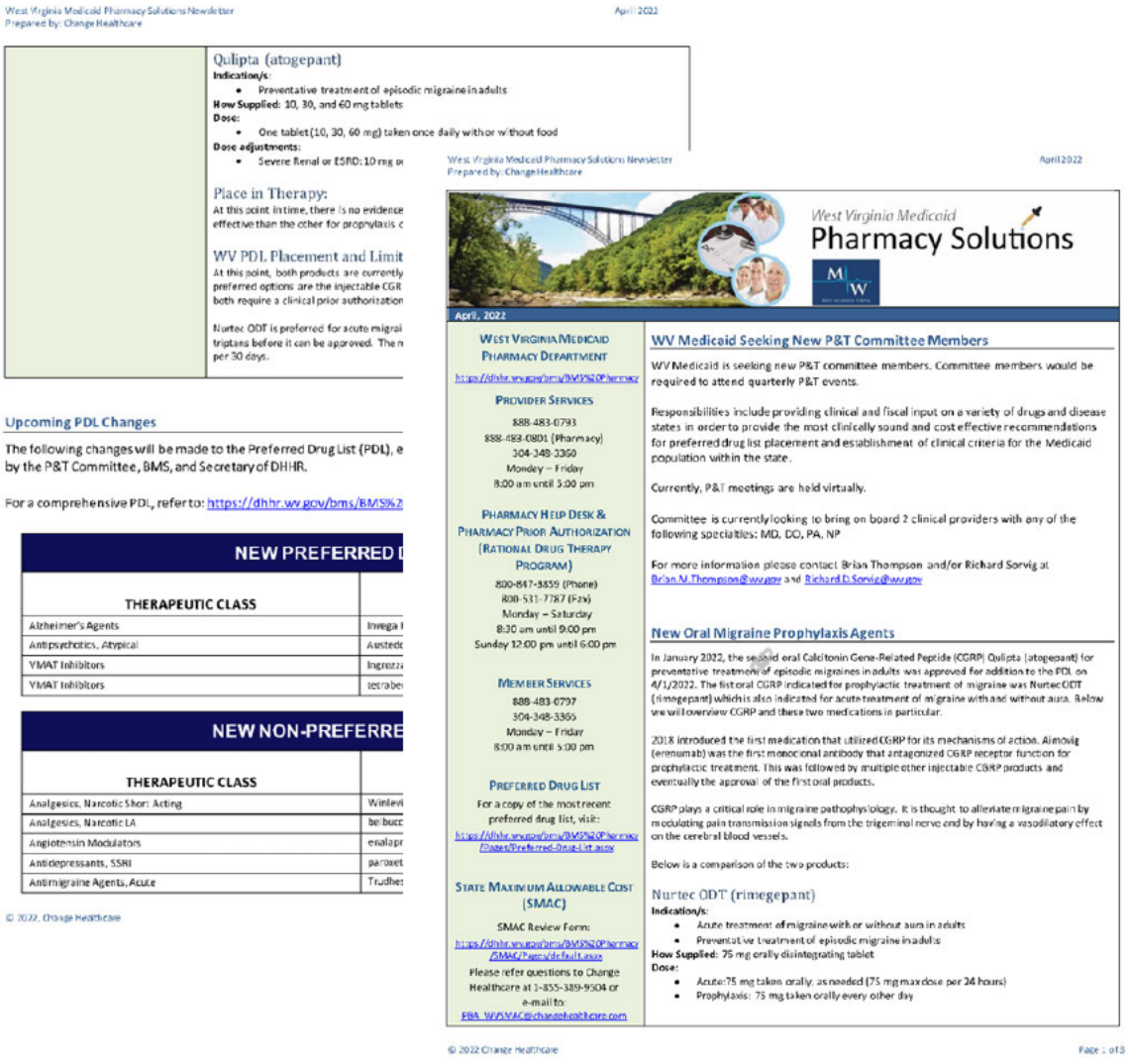
4.1.22.8 Other data files when identified that support the PDL, PPL, and SMAC programs quarterly

Change Healthcare will create and distribute data files relating to the PDL, PPL and SMAC programs in the format and timeline specified by the BMS. Change Healthcare understands any files that are due weekly are due by the close of business on Wednesday, quarterly files are due by the last day of the last month in the quarter, and 'as-needed' files are due within 72 hours of the initial request.

4.1.23 Vendor shall develop and create quarterly newsletters containing information relating to changes to the PDL, PPL and other pharmacy program matters in a file format that is compatible with West Virginia Office of Technology's currently supported operating platforms (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx to be displayed on BMS's https://dhhr.wv.gov/bms/Pages/default.aspx website for interested parties.

Vendor shall provide the electronic final version that will be displayed on BMS website.

Change Healthcare develops clinical newsletters for multiple clients, including BMS. The account manager along with the team of physicians and clinicians provide timely, relevant information for inclusion in the newsletter and will continue collaborating with the BMS to ensure all content is acceptable prior to distribution. The final version will be provided to BMS in an electronic file format that is compatible with their current supported version of Google Workspace. The following is a recent example of the newsletter for West Virginia, please note the information included in the newsletter is public information and does not include any PHI or confidential information.



West Virginia Medicaid Pharmacy Solutions Newsletter
Prepared by: Change Healthcare
April 2022

Qulipta (atogepant)
Indication/s:
- Preventative treatment of episodic migraine in adults

How Supplied: 10, 30, and 60 mg tablets
Dose:
- One tablet (10, 30, 60 mg) taken once daily with or without food

Dose adjustments:
- Severe Renal or ESRD: 10 mg p

Place in Therapy:
At this point in time, there is no evidence
effective than the other for prophylaxis c

WV PDL Placement and Limit
At this point, both products are currently
preferred options are the injectable CGR
both require a clinical prior authorization

Nurtec ODT is preferred for acute migrai
triptans before it can be approved. The n
per 30 days.

Upcoming PDL Changes

The following changes will be made to the Preferred Drug List (PDL), e
by the P&T Committee, BMS, and Secretary of DHHR.

For a comprehensive PDL, refer to: https://dhhr.wv.gov/bms/BMS%2

NEW PREFERRED D

THERAPEUTIC CLASS	
Alzheimer's Agents	Invega
Antipsychotics, Atypical	Austedo
VMAT Inhibitors	Ingrezz
VMAT Inhibitors	tetrabe

NEW NON-PREFERRE

THERAPEUTIC CLASS	
Analgesics, Narcotic Short Acting	Winlev
Analgesics, Narcotic LA	belbuca
Angiotensin Modulators	enalapr
Antidepressants, SSRI	paroxet
Antimigraine Agents, Acute	Trudhe

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West Virginia Medicaid Pharmacy Solutions Newsletter
Prepared by: Change Healthcare
April 2022

West Virginia Medicaid
Pharmacy Solutions

April, 2022

WEST VIRGINIA MEDICAID PHARMACY DEPARTMENT
https://dhhr.wv.gov/bms/BMS%20Pharmacy

PROVIDER SERVICES
888-483-0793
888-488-0801 (Pharmacy)
304-348-3360
Monday – Friday
8:00 am until 5:00 pm

PHARMACY HELP DESK & PHARMACY PRIOR AUTHORIZATION (RATIONAL DRUG THERAPY PROGRAM)
800-847-3859 (Phone)
800-531-7787 (Fax)
Monday – Saturday
8:30 am until 9:00 pm
Sunday 12:00 pm until 6:00 pm

MEMBER SERVICES
888-483-0797
304-348-3365
Monday – Friday
8:00 am until 5:00 pm

PREFERRED DRUG LIST
For a copy of the most recent preferred drug list, visit:
https://dhhr.wv.gov/bms/BMS%20Pharmacy/Pages/Preferred-Drug-List.aspx

STATE MAXIMUM ALLOWABLE COST (SMAC)
SMAC Review Form:
https://dhhr.wv.gov/bms/BMS%20Pharmacy/SMAC/Pages/default.aspx
Please refer questions to Change Healthcare at 1-855-389-9504 or e-mail to:
BBA_WVSMAC@changehealthcare.com

WV Medicaid Seeking New P&T Committee Members

WV Medicaid is seeking new P&T committee members. Committee members would be required to attend quarterly P&T events.

Responsibilities include providing clinical and fiscal input on a variety of drugs and disease states in order to provide the most clinically sound and cost effective recommendations for preferred drug list placement and establishment of clinical criteria for the Medicaid population within the state.

Currently, P&T meetings are held virtually.

Committee is currently looking to bring on board 2 clinical providers with any of the following specialties: MD, DO, PA, NP

For more information please contact Brian Thompson and/or Richard Sorvig at Brian.M.Thompson@wv.gov and Richard.D.Sorvig@wv.gov

New Oral Migraine Prophylaxis Agents

In January 2022, the second oral Calcitonin Gene-Related Peptide (CGRP) Qulipta (atogepant) for preventative treatment of episodic migraines in adults was approved for addition to the PDL on 4/1/2022. The first oral CGRP indicated for prophylactic treatment of migraine was Nurtec ODT (rimegepant) which is also indicated for acute treatment of migraine with and without aura. Below we will overview CGRP and these two medications in particular.

2018 introduced the first medication that utilized CGRP for its mechanisms of action. Aimovig (erenumab) was the first monoclonal antibody that antagonized CGRP receptor function for prophylactic treatment. This was followed by multiple other injectable CGRP products and eventually the approval of the first oral products.

CGRP plays a critical role in migraine pathophysiology. It is thought to alleviate migraine pain by modulating pain transmission signals from the trigeminal nerve and by having a vasodilatory effect on the cerebral blood vessels.

Below is a comparison of the two products:

Nurtec ODT (rimegepant)
Indication/s:
- Acute treatment of migraine with or without aura in adults
- Preventative treatment of episodic migraine in adults

How Supplied: 75 mg orally disintegrating tablet
Dose:
- Acute: 75 mg taken orally, as needed (75 mg max dose per 24 hours)
- Prophylaxis: 75 mg taken orally every other day

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Page 1 of 3

Figure 4: Sample State Newsletter

4.1.24 Vendor shall assist and fully cooperate with BMS in the implementation of the contract executed from this RFQ upon effective date of the contract.

4.1.24.1 Vendor should submit with their quotation and must be submitted prior to award an Implementation Plan that demonstrates the Vendor's ability to assume the responsibilities for BMS PDL, PPL, and SMAC programs upon award of this contract. There will be a two (2) month implementation period.

As the incumbent, Change Healthcare is already providing most of these services and will continue to do so seamlessly. If needed for the expanded scope, Change Healthcare has developed a draft project continuation plan (referred to as a project work plan) for the BMS project and included as Appendix C of this response.

The draft work plan includes tasks related to the continuation of the solution. The draft work plan also lists which teams are responsible for the work contained therein, whether it be Change Healthcare or BMS team members. Estimated durations provided are based on experience on other engagements.

The draft project plan will be refined and elaborated upon the project kickoff to ensure that the full project team agrees on resources, tasks, and durations for the transition project.

The project work plan is a living document that will be updated appropriately throughout the project lifecycle. Change Healthcare will manage the plan throughout the project and provide periodic updates to BMS on a mutually agreed-upon frequency. Typically, Change Healthcare provides updates no less frequently than bi-weekly, and sometimes weekly depending on the project phase. The project work plan defines the project management procedures proposed to be utilized by Change Healthcare for the duration of BMS' project. The overall approach to project management follows the PMI® PMBOK® Guide. The Change Healthcare project management plan defines the approach in the following areas:

- Integration management
- Scope management
- Schedule management
- Cost management
- Quality management
- Communications management
- Procurement management
- Stakeholder management

In addition to the comprehensive project management plan, Change Healthcare will also provide a series of standalone management plans that address other critical elements of the project. These plans are defined in the next table where bulleted items list the critical deliverables. Each plan will include other content as agreed upon with BMS.

Project Plan	Explanation
CMS Certification Plan	• Defines certification project approach • Highlights certification specific deliverables and artifacts • Establishes roles and responsibilities for certification • Delineation of evidence between R2 and R3 review • Certification Evidence Package Templates

Project Plan	Explanation
Change Management Plan	• Will utilize BMS's operation portal with centralized Information Technology Service Management (ITSM) capabilities • Records requested changes to approved plans to a log • Determines/evaluates the impact of requested changes • Employs a systematic approval process • Implements approved changes • Records decisions made/reasons for decisions and communicate decisions across stakeholders • Typical events that trigger the change management process • Approach to testing all changes to solution functionality

Documentation Management Plan	• Describes the Electronic Document Management System (EDMS) solution, a collection of technologies that work together to provide a comprehensive solution for managing the creation, capture, indexing, storage, retrieval, and disposition of artifacts from both paper and electronic sources
	• Describes usage of the EDMS solution in several processes/applications, including Med Management tool, Drug Rebate, and Prior Authorization processes
	  ○ Imaging Management – This element will be used for hard-copy (paper) artifacts during the conversion process, as well as in everyday operational activities when paper is presented
	  ○ Document Management – This element is used to store electronic objects, and an index for quick artifact identification and retrieval of information from artifact libraries
	  ○ Enterprise Report Management – This element is used to electronically capture, index, burst, distribute, and store system-generated reports and documents
	• Document location approach allows for a single entry to search and retrieve
	• Plan can be expanded to encompass the needs of the solution

Project Plan	Explanation
Configuration Management Plan	• Will utilize the client's operation portal with centralized Information Technology Service Management (ITSM) capabilities • Describes Roles and Responsibilities • Identifies configuration management processes with distinct development libraries and system instances, ensure strict control of each component of the system so that the integrated system components match and remain in sync while in development • Describes the methodology of system maintenance and version control to the system's technical components, business rules and data stores is applied to ensure that the environment is sound and harmonized with system development, user acceptance test and production activities • For every module, the configuration items are stored in a central repository
Problem Management	• The practice of reducing the likelihood and impact of incidents by identifying actual and potential causes of incidents and managing workarounds and known errors. • Will utilize client's operation portal with centralized Information Technology Service Management (ITSM) capabilities • Defines roles and responsibilities • Defines approach to Problem Management • Escalation procedure • Logs all Problems that impact schedules, scope expected effort, or another dimension of the project • Investigation, Diagnosis, Work-around and Resolution • Resolves Problems and prevents re-occurrence • Timely management of Problems to avoid delays/risks • Tracks all components (Problem, staff assigned, due date, recommended solution) through completion

Project Plan	Explanation
Incident Management	• Unplanned interruption to a service or reduction in quality of a service • Will utilize client's operation portal with centralized Information Technology Service Management (ITSM) capabilities • Defines roles and responsibilities • Defines approach to isolated Incident Management. If not isolated, follow Problem Management Plan • Guides incident-related activities throughout the life of the project • Escalation procedure for quick restore of service operations • Logs all incidents that impact schedules, scope expected effort, or another dimension of the project • Resolves Incidents quickly and prevents re-occurrence • Timely management of Incidents to avoid delays/risks • Tracks all components (incident, staff assigned, due date, recommended solution) through completion
Business Continuity, Disaster Recovery, and Contingency Plan	• Previous iterations of Change Healthcare's claims processing solution required physical servers that were in one of two separate data centers to provide, and support, disaster recovery/business continuity (DR/BC) initiatives. While this method was the industry standard, annual testing to demonstrate a successful failover and return to production takes hours and is not very efficient in terms of resources, costs, or time. Traditional approaches to DR/BC are outmoded and insufficient considering complex technology and system platforms in use today. • Change Healthcare's new cloud-based platform utilizes Chaos Engineering to identify and, subsequently, address previously undetected issues prior to them causing an outage or failure. This approach has been adopted and further developed into the process used today by IT organizations, including Change Healthcare, around the world. The idea is not to create chaos or disrupt the system but prevent turmoil from happening. • Plan is stored in a secured cloud data repository • Objective is to meet the specified Recovery Time Objective (RTO) as set forth by the business unit • Describes communications required for BC/DR • Defines roles and responsibilities • Describes the procedures and sequencing of steps required for recovery and validation

Project Plan	Explanation
Data Conversion Management Plan	• Defines Change Healthcare's approach to converting data from the legacy system • Defines the file types and record layouts used in the Change Healthcare solution • Defines how BMS will review converted data for accuracy • Identifies critical predecessors for conversion readiness • Identifies stakeholders and roles and responsibilities for the conversion process
Implementation Plan	• Describes the activities directly associated with the cutover to the new system • Provides a schedule of every PBM implementation activity • Identifies resources for performing each activity and the resource confirming completion • Finds triggers for invoking a contingency activity • Includes call tree for notification of successful completion of steps and/or invoking of a contingency activity
Interface Management Plan	• Defines business process used to execute and validate interfaces • Identifies stakeholders and roles and responsibilities for the conversion process • Identifies the escalation path in the event of an interface failure • Provides approach to defining interface structure
Staffing Plan	• Identifies Key Staff and necessary supervisory and support staff • Work location • Work schedule • Reporting structure for all staff supporting contract • Resumes for staff supporting contract and job descriptions for all positions • Defines project organization and documents its evolution throughout the project • Defines project staffing requirements by skill and function • Identifies and assigns appropriate internal resources to project roles • Monitors staff and assignments in conjunction with the project plan • Typically updated on an annual basis

Project Plan	Explanation
Test Management Plan	• Scope of testing • Defines types of testing that will occur (system, integration, load, and stress) • Defines the roles and responsibilities of the teams that will support testing • Defines defect management approach • Testing tools to be used • Reporting expectations • Definition of Test Environments • Unit Test Plan (including a description of test data, testing process, and expected results)
Training Plan	• Operations training approach • Description of all training materials to be provided • Training subject areas • Establish an approach for refresher training • Location of training
Transition Plan	• Created upon completion of implementation and BMS sign-off on final project deliverables • Includes a comprehensive list of tasks and activities to be delivered to the Account Manager for ongoing upkeep • Coordinates services/how services will be maintained throughout • Documents: • Schedule of transition activities • Transfer of documentation, files, and other records • Operational resource requirements • Tasks/subtasks for the transition process

4.1.24.2 Vendor's Implementation Plan must describe major task assignments considered to meet PDL, PPL, and SMAC program services, including, but not limited to: project start-up, project status, project updates, and project reassignments. John Estey

As the incumbent, Change Healthcare is uniquely positioned to meet this requirement as these services and supporting solution are already in place.

The attached project work plan (PWP) provided as Appendix C of this proposal response, outlines a review process for each of these existing

services to confirm that they are meeting the needs of BMS and to identify any opportunities.

4.1.24.3 Vendor shall attend a meeting, scheduled by BMS within five (5) working days of contract award, with BMS staff and Vendor's key staff and other support staff to initiate the contract deliverables and services. This meeting shall be conducted either in person or virtually, as agreed upon by Vendor and BMS.

As the incumbent, Change Healthcare is already providing most of these services and will continue to do so seamlessly. If needed for the expanded scope, Change Healthcare is prepared to collaborate with BMS to schedule a project start-up meeting to be conducted within five business days of the contract effective date. Change Healthcare will submit an agenda for BMS review and approval no later than five business days prior to the meeting. An adequate start-up meeting ensures that the project team and stakeholders have a shared understanding of scope, goals, known risks, and high-level timeline.

This collaborative event will set the foundation of a trusted partnership that will carry the teams through full implementation.

Change Healthcare has found that the following agenda items helped build a high-level framework that has made every project kick-off meeting a success.

1. Introductions, to include but may not be limited to:
   - Key Change Healthcare team members who will provide an overview of their functional area, including management-level representative for the start-up phase
   - Key BMS staff who will provide their overview
2. Executive summary
3. Scope and deliverables
4. Roles and responsibilities
5. Timelines
6. Communication and meeting plans
7. Questions
8. Next steps

4.1.25 Vendor shall assist and fully cooperate with BMS when transitioning to a new Vendor at the end of the contract executed from this RFQ.

Upon completion of Change Healthcare's contract for BMS, Change Healthcare works with the incoming vendor and BMS to provide a controlled turnover of data, documentation, file layouts, and non-proprietary code at no cost to BMS based on the turnover plan provided during implementation of the project. Change Healthcare understands its responsibility for the orderly transition of

work and the accuracy of data in coordination with BMS, and the incoming vendor.

4.1.25.1 Vendor shall provide a Close-Out and Turnover Plan electronically that identifies the Vendor's approach, tasks, staffing, and schedule for turnover of contract responsibilities.

Change Healthcare will provide an electronic Close-Out and turnover plan detailing approach, tasks, staffing, and schedule of turnover activities. An initial turnover plan will be submitted to BMS during the last year of the base contract. Change Healthcare will submit to BMS a written report prior to the end of the contract detailing the status of any open work orders at that time. Change Healthcare will submit a finalized turnover work plan, based on BMS' comments to the initial turnover work plan. The approach to contract turnover is similar to Change Healthcare's implementation approach; close collaboration with BMS, and the incoming vendor to ensure minimal impact of services for the members.

During a turnover plan from Change Healthcare to the successor vendor or BMS, appropriate reporting and status updates will be provided throughout the turnover process and in closing. Change Healthcare will utilize the standard suite of reports to bring transparency of the project to the team. Change Healthcare will work in partnership with the successor vendor and BMS to agree on the reporting that will be most helpful to the entire turnover team. This process will include but may not be limited to:

- Overall project health
- Project work plan updates, including a summary of updates and activities for the reporting period and scheduled and anticipated activities for the upcoming reporting period
- Plan updates for the reporting period
- Escalated risks and risk avoidance responses for the agreed reporting period
- Escalated issue and issue resolution plans for the agreed reporting period
- Technical assistance from all relevant areas of the business
- All standard policies, procedures, and documentation will be tracked for appropriate transition to the successor vendor and BMS
- Training plan to include training areas as well as training material

To work through a successful turnover plan, Change Healthcare leverages its project management standards. This includes but may not be limited to a full and capable project plan, risk planning, communication planning, training needs, documentation requirements, and overall project health reporting.

All departmental areas will work through the transition of the project to the incoming vendor. By approaching the turnover plan in the same way as

the takeover plan, Change Healthcare can deliver a smooth transition to the new vendor.

4.1.25.2 Vendor will submit the Close-Out and Turnover Plan to BMS for approval within thirty (30) calendar days of receiving BMS notification to initiate the Close-Out and Turnover Phase of the expiring contract.

An initial turnover plan will be submitted to BMS during the last year of the base contract. Change Healthcare will submit to BMS a written report prior to the end of the contract detailing the status of any open work orders at that time. Change Healthcare will submit a finalized turnover work plan, based on BMS' comments to the initial turnover work plan. The approach to contract turnover is similar to Change Healthcare's implementation approach; close collaboration with BMS, and the incoming vendor to ensure minimal impact of services for the members.

4.1.25.3 Vendor shall dedicate resources consistent with the approved Close-Out and Turnover Plan.

Change Healthcare's team includes the Turnover Project Manager, Security Officer, Privacy Officer, Drug Rebate Processing Expert as well as SMEs and key operations staff to participate in testing during the turnover phase.

4.1.25.4 Upon request, Vendor shall transfer to BMS ownership all data collected, created, summarized, and/or aggregated, and all deliverables and reports created specifically for BMS during the contract period.

In addition to the General Terms and Conditions, Change Healthcare agrees the BMS owns its data. Change Healthcare maintains ownership of its proprietary information, trade secrets and Intellectual property. Change Healthcare understands its performance and service obligations during the turnover phase as outlined in the terms and conditions of the contract. In the event a replacement vendor is selected as the result of a future procurement, Change Healthcare remains a trusted partner while executing a seamless handoff. Change Healthcare is prepared to meet all deliverables for BMS, as required, through the turnover period. Upon contract award, and through implementation, Change Healthcare collaboratively discusses these expectations with BMS to ensure understanding and agreement in line with that of BMS.

4.1.25.4.1 Data, deliverables, and reports shall be transferred in a file format that is compatible with West Virginia Office of Technology's currently supported operating platforms (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx

As required through successor Contractor File Transfer Schedule, Change Healthcare will transfer files to BMS and/or successor

contractor. Additionally, four weeks after receipt of successor, Change Healthcare will outline a Takeover Two-way File Transfer Implementation Plan.

4.1.25.4.2 Data, deliverables, and reports will be transferred in accordance with a schedule and in an electronic format, no longer than thirty (30) calendar days prior to the end of the contract.

Change Healthcare understands its performance and service obligations during the turnover phase as outlined in the terms and conditions of the contract. In the event a replacement vendor is selected as the result of a future procurement, Change Healthcare remains a trusted partner while executing a seamless handoff. Change Healthcare is prepared to meet all deliverables for BMS, as required, through the turnover period. Upon contract award, and through implementation, Change Healthcare collaboratively discusses these expectations with BMS to ensure understanding and agreement in line with that of BMS.

The Turnover Schedule below provides a summary by turnover phase, milestones, deliverables, and tasks identified.

CATEGORY	DELIVERABLE or MILESTONE
PHASE: TURNOVER START-UP	
Turnover Project Management	12 months prior to Last Day of Operations (LDO): • Assemble turnover management team • Submit turnover management team name, resumes, roles, and responsibilities • Submit turnover work plan (R) • Submit turnover project control and reporting deliverables and process (R) • Submit project control and reporting deliverables and process (r) • Submit updated turnover work plan (R) 11 months prior to LDO: • Submit turnover communication management plan (R) • Submit issue and risk management plan (R) • Implement issue and risk tracking system
Turnover Requirements Operations	12 months prior to LDO: • Submit current inventory of all supplies and informing materials (R)

CATEGORY	DELIVERABLE or MILESTONE
	• Submit list of PO boxes, phone numbers, facsimile numbers, and related information • Submit current inventory list of all files • Submit manual and documentation maintenance methodology • Submit inventory list of all manuals and related documentation (R) • Submit complete set of manuals and related documentation (R)
Turnover Requirements	12 months prior to LDO: • Submit job roster (R) • Coordinate job seminars with successor contractor • Submit cost reimbursed hardware, software, and equipment list • Submit turnover administrative procedures manual (R)
PHASE: LDO PREPARATION	
Turnover Training	Six weeks prior to Turnover Training: • Submit turnover training plan
Turnover Requirements Operations	11 months prior to LDO: Submit proposed Master Index of Records format ten months prior to LDO: • Submit reports inventory • Submit operational performance statistics as requested by BMS (R) • Submit master index of records (R) As required through successor Contractor File Transfer Schedule: • Transfer files to BMS and/or successor contractor Four weeks after receipt of successor Contractor Takeover Two-way File Transfer Implementation Plan: o Submit Turnover Two-way File Transfer Implementation Plan
Turnover Requirements	11 months prior to LDO: • Conduct facility tours (R) Ten months prior to LDO: • Submit configuration documentation
PHASE: TURNOVER TRAINING	

CATEGORY	DELIVERABLE or MILESTONE
Turnover Training	Nine months prior to LDO: • Conduct turnover training During Turnover Training: • Submit turnover training progress report (R) • Submit turnover training evaluations (R) • Turnover training sign-up and attendance list (R)
PHASE: TURNOVER TESTING SUPPORT	
Turnover Testing Support	In preparation and during successor contractor takeover testing: • Provide testing support as requested • Provide files and documentation as requested • Provide statistics as requested by BMS
PHASE: PRE-LDO and TURNOVER PHASE-OUT	
Turnover Operations	As required through successor Contractor File Transfer Schedule: • Transfer files to BMS and/or successor contractor
Pre-LDO	Implement monitoring activities: • Coordinate dependent activities with BMS and successor contractor Four months prior to LDO: • Submit turnover phase-out plan
PHASE: LDO	
Turnover Requirements Operations	Through LDO Phase: • Monitor and provide status to BMS Two weeks prior to LDO: • Submit all BMS publications At LDO: • Submit remaining inventory of all cost- reimbursed informing materials • Submit the body of records identified in the Master Index of Records As required through successor Contractor File Transfer Schedule
Last Day of Operations Phase	• Transfer BMS operations to the successor contractor

CATEGORY	DELIVERABLE or MILESTONE
	• Transfer unprocessed forms. Program records and update files to the successor contractor • Transfer all cost-reimbursed software and equipment to the successor contractor • Transfer all associated software, supplies, operating manuals, maintenance agreements to successor contract • Transfer all network communication • Transfer all reporting • Provide LDO-reporting to BMS
PHASE: POST-LDO and TURNOVER CLOSEOUT	
Turnover Requirements Operations	As required through successor Contractor File Transfer Schedule: • Transfer files to BMS and/or successor contractor
Post-LDO Requirements	• Provide post-LDO reporting to BMS • Complete post-LDO and turnover closeout requirements

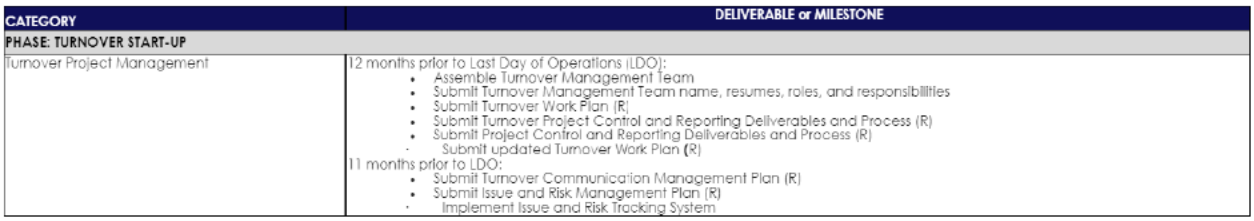
Table 1: Turnover Milestone and Deliverables

4.1.25.4.3 Vendor shall provide a Turnover Results Report which documents the completion and results of each task identified in the Turnover Plan.

During the close-out phase of the turnover process, Change Healthcare will supply a comprehensive report of the last day of operations expectations and approvals. This turnover report will encompass a variety of documentation including a completed work plan and deliverables sign off.

4.1.25.4.4 The Turnover Results Report shall be submitted in a file format that is compatible with West Virginia Office of Technology's currently supported operating platforms (presently Google Workspace), https://technology.wv.gov/Pages/default.aspx

Change Healthcare will provide the report in a file format that is compatible with West Virginia Office of Technology.



CATEGORY	DELIVERABLE or MILESTONE
PHASE: TURNOVER START-UP	
Turnover Project Management	12 months prior to Last Day of Operations (LDO): • Assemble Turnover Management Team • Submit Turnover Management Team name, resumes, roles, and responsibilities • Submit Turnover Work Plan (R) • Submit Turnover Project Control and Reporting Deliverables and Process (R) • Submit Project Control and Reporting Deliverables and Process (R) • Submit updated Turnover Work Plan (R) 11 months prior to LDO: • Submit Turnover Communication Management Plan (R) • Submit Issue and Risk Management Plan (R) • Implement Issue and Risk Tracking System

Figure 5: Sample Turnover Plan

4.1.25.4.5 The Turnover Results Report shall be submitted in accordance with a schedule approved by BMS, no later than thirty (30) calendar days prior to the end of the contract.

Change Healthcare's approach to a contract turnover plan mirrors the implementation approach. Change Healthcare remains in close collaboration with the client and new vendor to produce a successful turnover plan. The expectation is that any successor cooperates fully with Change Healthcare to make sure that BMS and members have no interruptions in services. Change Healthcare is committed to supporting BMS during the turnover phase of the project by tracking project processes to include risks, timelines, status reports, and other activities that may be occurring within the turnover phase, including the development of the completion certification and all associated documentation.

4.1.26 Additional Services-Vendor shall provide a pool of hours annually that can be used by BMS for assistance, advice, and consultation for Medicaid pharmacy activities, such as additional clinical consultation, reports related to the PDL, PPL, HCPADL, and SMAC, or pricing of a complex nature, direct contact by telephone or by other agreed upon means to prescribers regarding appropriate drug utilization. Vendor shall provide on the Pricing Page the all-inclusive hourly rate for additional services requested by BMS during each of the possible Contract years. The one hundred (100) hour pool is an estimate only; actual quantities requested by BMS during the life of contract may vary. Vendor shall include in the Pricing Page the cost of additional services. This will be computed by multiplying the all-inclusive hourly rate by one hundred (100) [Estimated] as per section 4.1.26.

Change Healthcare’s pricing is an all-inclusive hourly rate for additional services requested by BMS during each of the contract years. Change Healthcare understands the 100 hours is an estimate only and actual hours requested by BMS throughout the entirety of the project may vary.

4.1.27 Vendor shall agree to be bound by all Service Level Agreements listed in Exhibit B, Service Level Agreements.

Change Healthcare has reviewed and understands the Service Level Agreements listed in Exhibit B of the RFQ and will comply with the requirements.

5. CONTRACT AWARD:

5.1 Contract Award: The Contract is intended to provide Agency with a purchase price for the Contract Services. The Contract shall be awarded to the Vendor that provides the Contract Services meeting the required specifications for the lowest overall total cost as shown on the Pricing Page.

5.2 Pricing Page: Vendor should complete the Pricing Page by submitting pricing for the following items: Startup Costs; Annual Not To Exceed Costs; and Additional Services. Vendor should complete the Pricing Page in full as failure to complete the Pricing Page in its entirety may result in Vendor's bid being disqualified.

Vendor should type or electronically enter the information into the Pricing Page through wvOASIS, if available, or as an electronic document. Instructions for completing the pricing page can be found in Exhibit A.

6. PERFORMANCE: Vendor and Agency shall agree upon a schedule for performance of Contract Services and Contract Services Deliverables, unless such a schedule is already included herein by Agency. In the event that this Contract is designated as an open-end contract, Vendor shall perform in accordance with the release orders that may be issued against this Contract.

7. PAYMENT: Agency shall pay monthly in arrears, as shown on the Pricing Page, for all Contract Services performed and accepted under this Contract. Vendor shall accept payment in accordance with the payment procedures of the State of West Virginia.

8. TRAVEL: Vendor shall be responsible for all mileage and travel costs, including travel time, associated with performance of this Contract. Any anticipated mileage or travel costs may be included in the flat fee or hourly rate listed on Vendor's bid, but such costs will not be paid by the Agency separately.

9. FACILITIES ACCESS: Performance of Contract Services may require access cards and/or keys to gain entrance to Agency's facilities. In the event that access cards and/or keys are required:

9.1 Vendor must identify principal service personnel which will be issued access cards and/or keys to perform service.

9.2 Vendor will be responsible for controlling cards and keys and will pay replacement fee, if the cards or keys become lost or stolen.

9.3 Vendor shall notify Agency immediately of any lost, stolen, or missing card or key.

9.4 Anyone performing under this Contract will be subject to Agency's security protocol and procedures.

9.5 Vendor shall inform all staff of Agency's security protocol and procedures.

10 VENDOR DEFAULT:

10.1 The following shall be considered a Vendor default under this Contract.

10.1.1 Failure to perform Contract Services in accordance with the requirements contained herein.

10.1.2 Failure to comply with other specifications and requirements contained herein.

10.1.3 Failure to comply with any laws, rules, and ordinances applicable to the Contract Services provided under this Contract.

10.1.4 Failure to remedy deficient performance upon request.

10.2 The following remedies shall be available to Agency upon default.

10.2.1 Immediate cancellation of the Contract.

10.2.2 Immediate cancellation of one or more release orders issued under this Contract.

10.2.3 Any other remedies available in law or equity.

11 MISCELLANEOUS:

11.1 Contract Manager: During its performance of this Contract, Vendor must designate and maintain a primary contract manager responsible for overseeing Vendor's responsibilities under this Contract. The Contract manager must be available during normal business hours to address any customer service or other issues related to this Contract. Vendor should list its Contract manager and his or her contact information below.

Contract Manager: **Ryan Fell**

Telephone Number: **304-278-4764**

Fax Number:

Email Address: **Ryan.Fell@changehealthcare.com**

APPENDIX

A. Change Healthcare Client Listing

B. Resumes

C. Project Work Plan

D. Sample Therapeutic Class Review

Change Healthcare Client Listing

Services Provided	Pharmacy Claims Adjudication	Drug Rebate Invoicing	SR Negotiations – Multi-State Pool or Single-State	Prospective DUR	Retrospective DUR	PDL / Formulary Management	Prior Authorizations	Help Desk / Call Center	Pharmacy Payments	Clinical Consulting / Drug Class Reviews	TPL / COB	P&T Committee / DUR Board Support	Provider Enrollment / Eligibility Verification	Reporting and Analytics	MTM / PCM / IBM	SMAC	RAC / Program Integrity
Delaware SR (05/2015 – 06/2022)			✓					✓		✓		✓		✓			
Illinois PBMS (03/2014 -03/2024)	✓	✓		✓	✓	✓	✓	✓						✓		✓	
Iowa POS (06/2005 – 06/2022)	✓	✓	✓	✓	✓			✓						✓			
Iowa Clinical (07/2004 – 06/2022)						✓	✓	✓		✓		✓		✓	✓		
Maine POS (MEPOPS) (04/1995 – 09/2022)	✓		✓	✓	✓	✓	✓	✓		✓		✓		✓	✓	✓	✓
Maine ADAP/TB (11/2002 –09/2022)	✓	✓				✓	✓	✓	✓				✓	✓			
Maine Tobacco (12/2001 – 09/2022)	✓							✓					✓	✓			
Maine/DXC MedPA (2008 – 02/2023)							✓	✓		✓				✓			
Maine/DXC Radiology Benefit Management (2014 – 09/2022)							✓	✓		✓				✓			
Minnesota SMAC (06/2011 – 05/2023)								✓						✓		✓	
Mississippi Clinical (10/2011 – 6/2023)		✓	✓			✓	✓	✓		✓		✓		✓	✓		
New Jersey SUL (03/2011 – 06/2022)								✓						✓		✓	

CHANGE HEALTHCARE

Services Provided	Pharmacy Claims Adjudication	Drug Rebate Invoicing	SR Negotiations – Multi-State Pool or Single-State	Prospective DUR	Retrospective DUR	PDL / Formulary Management	Prior Authorizations	Help Desk / Call Center	Pharmacy Payments	Clinical Consulting / Drug Class Reviews	TPL / COB	P&T Committee / DUR Board Support	Provider Enrollment / Eligibility Verification	Reporting and Analytics	MTM / PCM / IBM	SMAC	RAC / Program Integrity
North Dakota SMAC (07/2011 – 06/2024)								✓						✓		✓	
North Dakota SR (05/2015 – 06/2024)			✓											✓			
Ohio PBM (07/2016 – 06/2023)	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓		✓	✓
Ohio BWC (2018-June 2022)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Oklahoma SR (02/2016 – 3/2023)			✓											✓			
Oregon SR (05/2011 – 3/2023)			✓											✓			
Pennsylvania PDL, Rebate & RDUR (01/2016 – 09/2023)		✓	✓		✓	✓		✓		✓		✓		✓			
SSDC Supplemental Rebate Pooling (01/2006 – 3/2023)			✓											✓			
Utah PBA (04/2011 – 12/2022)	✓		✓	✓		✓	✓	✓						✓			
Utah Rebate (01/2016 – 12/2022)		✓															
Vermont PBM (05/2014 - 12/2022)	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓			✓	✓	✓	
West Virginia Clinical (08/2008 –02/2023)			✓			✓				✓		✓		✓		✓	
Wyoming PBM (11/2008 – 12/2024)	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓

CHANGE HEALTHCARE

RYAN FELL

Regional Pharmacy Account Manager

SUMMARY OF EXPERIENCE

Have worked in the managed care industry for 8 years supporting Medicaid states in some capacity since the beginning of my career. Experience in account management, PDL, P&T, RDUR, and SMAC implementation and support. Also have extensive experience in utilization management within the Medicaid space.

I bring almost a decade of Medicaid specific experience to my role. Additionally, as a lifelong West Virginia resident, I bring a zeal towards clinically and fiscally supporting the Medicaid population within the state.

EMPLOYMENT

2020 – Present Regional Pharmacy Account Manager
Change Healthcare, Morgantown, WV (Remote)

- Responsible for managing and maintaining the relationship with Delaware, Minnesota, North Dakota, New Jersey, Pennsylvania, and West Virginia Medicaid PDL/RDUR/SMAC accounts
- Provides clinical and administrative services related to preferred drug list (PDL), supplemental rebate (SR), state maximum allowable cost (SMAC), RetroDUR, pharmaceutical and therapeutics (P&T) committee support, file transfers and maintenance, preparation of weekly drug file and post-P&T committee meeting updates, maintenance for preferred drug list including budgetary and clinical reports
- Works with pharmacy benefits administration (PBA) medical, clinical, and analytics staff to analyze and forecast drug trends, summarize data, and prepare reports
- Participates in disaster recovery plan preparation, updates, tests, and real disaster recovery operations
- Oversees operations of any contractual duties including service level agreements (SLAs) and deliverables. Responsible for monitoring and adhering to contract SLAs for each state account
- Supports the Business Development Team as a subject matter expert when needed to develop/review content for proposals as well as support product demonstrations

2017 – 2020 Clinical Pharmacist Product Management
Evolent Health, Morgantown, WV (Remote)

- Medicaid line of business support
  - Verified accurate implementation of change form requests for state files to PBA partners
  - Ensured member facing documents are accurate and up to date
  - Assisted line of business lead and team with UM policy updates, state file review, change form and coding implementation accuracy, managing override requests, clinical strategy, formulary management, PBA clinical relationship, and clinical benefits question responses.

- Performed utilization management reviews (prior authorization, step therapy, non-formulary, etc.) for all lines of business (Medicare, Medicaid, Commercial, Exchange)
- Ad hoc P&T committee monograph and policy development

2014 – 2017 Prior Authorization Specialist
Rational Drug Therapy, Morgantown, WV

- Provided prior authorization reviews for the Medicaid population of West Virginia
- Assistance in development of formulary and medication use criteria
- Developed and presented to West Virginia Department of Health and Human Resources a novel clinical program to address gaps in care for the Medicaid Foster Care children

EDUCATION

2010-2014 West Virginia University School of Pharmacy, Morgantown, WV

- Doctor of Pharmacy
- Cum Laude/ Deans Outstanding Achievement Award

PROFESSIONAL LICENSES, CERTIFICATIONS AND MEMBERSHIPS

Registered Pharmacist, WV Board of Pharmacy, 8/4/2014-6/30/2024, [redacted]

DR. LAUREEN BICZACK, DO

Chief Medical Officer

SUMMARY OF EXPERIENCE

As Chief Medical Officer, Dr. Biczak oversees all clinical aspects of Change Healthcare's programs. She has extensive experience working on the clinical and fiscal aspects of the pharmacy benefits for the Medicaid Agencies in multiple states. Prior to joining our team, she spent more than six years as the Medical Director for Maine's Medicaid program, MaineCare, at the Department of Health and Human Services. She brings to the table extensive experience in all aspects of Medicaid Programs, including PDL design and implementation, drug evaluations, prior authorizations and in-depth knowledge of policy and regulatory issues. She also has worked extensively with the medical prior authorization program for Maine Medicaid.

Dr. Biczak is board certified in Internal Medicine and Infectious Diseases. Her continued part-time clinical practice offers Change Healthcare a unique view of pharmacy issues – from both the State and provider perspective. Dr. Biczak is a member of the American College of Physicians, the Maine Medical and Maine Osteopathic Societies, and several professional Infectious Disease Societies. She has in the past served as a gubernatorial appointee to the Maine Quality Forum Advisory Committee, which is devoted to not only improving the quality of healthcare in Maine but also the transparency of that quality for Maine citizens.

She received her Doctor of Osteopathy from the University of New England College of Osteopathic Medicine.

EMPLOYMENT

2012 – Present Medical Director
Change Healthcare, Augusta, Maine

- Transition of company ownership in 2013 to Emdeon, roles and responsibilities fundamentally unchanged
- Actively host regular contacts between clinicians, disseminate clinical information, and encourage clinical interaction with updates on best practices, new drug reviews, and evidence-based learning
- Always maintain an atmosphere of evidence based clinical excellence and client centered service
- Provide clinical, fiscal and policy input as needed on all aspects of Medicaid or commercial activities by serving as a subject matter expert, attending meetings, and providing written or oral input

2007 – 2012 Associate Medical Director
Change Healthcare, Augusta, Maine

- Oversaw clinical aspects of the pharmacy benefits for the Medicaid Agencies in multiple states
- Recommended both pro-DUR and retro-DUR criteria and oversees clinical prior authorization activities
- Oversaw clinical and fiscal aspects of PDL design including supplemental rebate negotiation, and integration with State Maximum Allowable Cost activities

- Oversaw development of clinical therapeutic class and drug reviews
- Actively participated in the P & T and DUR meetings in multiple states
- Oversaw clinical aspects of pharmacy benefit care management services for Maine Medicaid including narcotic restriction programs and high-cost specialty pharmacy management
- Oversaw all clinical activities at CHC, including the medical and radiology benefit management services

2005 – 2007 Maine Medicaid MMIS Remediation Project Lead

Maine Department of Health and Human Services, Augusta, Maine

- Medical Director for the Maine Bureau of Medical Services (Medicaid Program)
  - Served as a voting member of the Drug Utilization Review Committee
  - Participated in clinical and fiscal aspects of PDL design and management activities
  - Participation in medical and pharmacy clinical determinations including fair hearings
  - Participated as a member of the Senior Management Team and was actively involved in all aspects of health care management activities including benefit design, including the pharmacy benefit, pay for performance initiatives, budgetary issues, interpretation of Federal Medicaid law, and quality projects
  - Consultant for coverage and medical necessity determinations, prior authorization and development of agency rules
  - Consultant for policy development, as well as coding and reimbursement determinations, including pharmacy policy
  - Served as the medical expert in the development of waivers
  - Communicated frequently with CMS and other States on a wide range of issues regarding MaineCare including pharmacy issues
  - Served as the liaison for the Department with professional associations, often publicly speaking at meetings and conventions on the Department's behalf
  - Responded on behalf of the Commissioner of Health and Human Services and the Governor to concerns and complaints from providers, legislators, and members
  - Testified at legislative hearings when requested by the Commissioner
  - Developed reports to support quality and programmatic activities
  - Participated in multiple quality related workgroups and committees
- Chaired Covered Services Team
  - Reviewed new services for coverage determinations and budgetary implications
- Created Code Committee which oversaw decision analysis around new or changed codes and dealt with complex coding issues

1996 – Present Infectious Disease Teaching Service

- Actively involved in teaching students, interns, residents and fellows (including Infectious Disease Fellows) in the clinical setting
- Direct patient care for hospitalized patients with infectious disease problems at three hospitals

1990 – Present Clinical Practice

- Infectious Diseases and Travel/Tropical Medicine direct patient care
  - Inpatient and outpatient settings

EDUCATION

1988 – 1990 University of Connecticut, Farmington, CT

- Clinical and Research Fellow, Infectious Disease Program
- Program Director: Sam T. Donta, MD

1986 – 1988 Osteopathic Hospital of Maine, Portland, ME

- Internal Medicine Residency
- Program Director: David A Weed, DO

1985 – 1986 Osteopathic Hospital of Maine, Portland, ME

- Rotating Internship
- Program Director: Jon Karol, DO

1981 – 1985 University of New England College of Osteopathic Medicine

- Doctor of Osteopathy
- Appointed to Sigma Sigma Phi (Osteopathic Honor Society)

1978 – 1981 University of Maine at Orono

- B.A., Zoology, Summa cum Laude
- Appointed to Phi Beta Kappa

PROFESSIONAL LICENSES, CERTIFICATIONS AND MEMBERSHIPS

- State of Maine, License #[redacted], Expiration 07/31/16
- American Osteopathic Board of Internal Medicine, Certificate #[redacted]
  - Internal Medicine, 03/1990
  - Infectious Disease, 1991
- American College of Physicians
- Maine Osteopathic Association
- American Osteopathic Association
- Maine Medical Association
- Infectious Disease Society of America
- HIV Medicine Association
- Northern New England Infectious Disease Society
- Southern Maine Osteopathic Medical Group

PROFESSIONAL APPOINTMENTS

- Chief of Staff, 1995-1997, *Brighton Medical Center*
- Chief of the Department of Medicine, 1993-1995 *Brighton Medical Center*
- Institutional Review Board, 1993-1995, *Brighton Medical Center*
- Staff Executive Committee, 1993-1997, *Brighton Medical Center*
- Chair, Infection Control Committee, 1990-1997, *Brighton Medical Center*
- Chair, Medical Quality Review Committee, 1995-1997, *Brighton Medical Center*
- Clinical Monitoring Committee, 1990-1997, *Brighton Medical Center*
- Chair, Antibiotic Agents Subcommittee, 1990-1993, *Brighton Medical Center*
- Library Monitoring Committee, 1996-1997, *Maine Medical Center*
- Physician's Information Services Committee, 1998-1999, *Maine Medical Center*
- Pharmacy and Therapeutics Committee, 1998-2002, *Maine Medical Center*
- Maine Quality Forum Advisory Committee, 2005-2007

DR. JEFFREY BARKIN, MD, DFAPA

Associate Chief Medical Officer

SUMMARY OF EXPERIENCE

Dr. Barkin has been employed as Associate Chief Medical Officer with Change Healthcare since 2010. He has maintained a private and forensic psychiatry practice since 1991, treating individuals with a variety of mood, anxiety, and psychotic disorders. Dr. Barkin has special expertise in clinical trial design and analysis, and is especially interested in applying evidence based best practices in administrative and legal settings. Prior to his current position, he served as Chair of the Maine Medicaid DUR Committee and Chair of the Psychiatric Work Group. He is currently President Elect of The Maine Medical Association, Immediate Past President of Tri-County Mental Health Services, and a Past President of the State of Maine Association of Psychiatric Physicians.

In his twelve years working with the Change Healthcare team, he has undertaken medical director responsibilities for Medicaid pharmacy programs in Maine, Vermont, Ohio, Iowa, Mississippi, West Virginia and has been involved in all clinical programs related to Medicaid at Change Healthcare, and actively participates in the development of clinical therapeutic class and drug reviews. He also has multiple years of experience in interpreting clinical trial data to help inform placement of products on preferred drug lists, as well as application of research methods and outcomes in numerous settings including administrative and legal. Dr. Barkin is also an active member of the clinical team which oversees pharmaceutical utilization for multiple client states, multi-state drug negotiation pool, and high cost (specialty) pharmacy services.

EMPLOYMENT

2009 – Present Associate Chief Medical Officer
Change Healthcare, Augusta, ME

- Oversees clinical aspects of Medical PA services for Maine Medicaid
- Provides medical director guidance to client states pharmacy clinical programs
- Participates in development of clinical therapeutic class and drug reviews
- Provides input to pharmacy and therapeutics and drug utilization review committees
- Recommend both ProDUR and RetroDUR criteria and oversee clinical prior authorization activities
- Twelve years of experience with medical director responsibilities for Medicaid pharmacy programs in Maine, Vermont, Ohio, Iowa, Mississippi, and West Virginia
- Involved in all clinical programs related to Medicaid at Change Healthcare;
- Multiple years of experience in interpreting clinical trial data to help inform placement of products on preferred drug lists
- Application of research methods and outcomes in numerous settings including administrative and legal
- Ongoing work in developing other (non-pharmacy) Medicaid programs
- Capable of applying medical analytics to assess population impact of pharmacy management strategies
- Developed a dose consolidation program for high-cost antipsychotics for multiple client states which demonstrated robust cost savings with no deleterious impacts on adherence and has presented results at national conferences

- Developed geographic modeling assessing differential utilization of opiates employing Dartmouth Atlas methodology
- Active member of clinical team which oversees pharmaceutical utilization for multiple client states, multi-state drug negotiation pool, as well as high cost (specialty) pharmacy services

2004 – Present **Private Practice**
Portland, ME

- Clinical & Forensic Psychiatry
- Health Care Policy
- Complex healthcare Analysis
- Consultation to Business
- Teaching.

2000 – 2004 **Partner, Neurology Associates of Eastern Maine**
Bangor, Maine

1998 – 1999 **Acadia Hospital/Eastern Maine Medical Center**
Bangor, Maine

1994 – 1998 **Department of Psychiatry**
The Medical Center of Central Massachusetts, Worcester, Massachusetts

1993 – 1994 **Addiction Psychiatrist**
Adcare Hospital Worcester, Massachusetts

1992 – 1993 **Attending Psychiatrist**
Charles River Hospital, West Chicopee, Massachusetts

1992 – 1993 **Mediplex Psychiatric Nursing Home Holyoke, MA**
Center for Human Development West Springfield, MA
Private Practice Springfield, MA

1991 – 1992 **Therapeutic Associates Longmeadow, MA**

1989 – 1991 **On-Call Services**
Griffin Hospital Derby, Connecticut

1989 – 1991 **On-Call Services**
Silver Hill Hospital, New Canaan, Connecticut

EDUCATION

- 1988 – 1991 Residency in Psychiatry – Yale University New Haven, CT
- 1987 – 1988 Internship, Internal Medicine – University Hospital Boston, MA
- 1983 – 1987 M.D. – Yale University School of Medicine New Haven, CT
- 1979 – 1983 B.A. – Swarthmore College, Swarthmore, PA
- Graduated with Distinction – Phi Beta Kappa, Sigma Xi

PROFESSIONAL LICENSES, CERTIFICATIONS AND MEMBERSHIPS

- Licensed physician in the States of Maine, Massachusetts, and Connecticut.
- 1996 Added Certification – Geriatric Psychiatry Certificate # [redacted]
- 1993 Board Certified in Psychiatry Certificate # [redacted]
- 1998 State of Maine Certificate # [redacted]
- 1991 State of Massachusetts Certificate # [redacted]
- 1989 State of Connecticut Certificate # [redacted]
- 1988 Diplomate NBME
- President, Maine Association of Psychiatric Physicians
- Board member, Maine Medical Association

PROFESSIONAL LICENSES, CERTIFICATIONS AND MEMBERSHIPS (continued)

- Board member, Tri-county Mental Health
- Chairman, Maine Psychiatric Work Group
- Chairman, Drug Utilization Review Board – State of Maine
- American Psychiatric Association
- American Society of Clinical Psychopharmacology
- American Neuropsychiatric Association
- Maine Medical Association
- Past Member, Maine State Board of Bar Examiners
- Founder, Maine Women's Mental Health list serve
- Founder & Director, Maine Psychiatric Journal Club

DR. JACQUELYN A. HEDLUND, M.D., M.S.

Associate Medical Director

SUMMARY OF EXPERIENCE

Dr. Jacquelyn Hedlund joined the Change Healthcare clinical team in 2015 and brings more than 27 years of relevant experience to our clinical team. She also currently holds the position of Assistant Medical Director at Community Health Options, one of the original not-for-profit health insurance cooperatives born out of the ACA.

Daily, she works closely with our Medical Directors and our clients, bringing innovative clinical expertise with her consultation to states including Iowa, Maine, Mississippi, Ohio, Pennsylvania, Vermont, and West Virginia. Her experience includes utilization management, prior authorization, PDL design and implementation, new drug evaluation, quality assurance, multidisciplinary program development and clinical trial implementation. Her industry knowledge, combined with real-world medical experiences benefit our Medicaid clients.

Jacquelyn is board certified in Internal Medicine and Hematology continues to be an active member in the clinical world. She has been in practice for 18 years, providing care to patient in Maine with benign and malignant hematologic conditions. She was the first Medical Director for the Maine Medical Center Cancer Institute and was instrumental in its conception and development. She continues her practice part-time at New England Cancer Specialists in southern Maine. She is a fellow of the American College of Physicians and a member of the American Society of Hematologists and the American Society of Clinical Oncologists.

She received her medical degree from the University of Vermont College of Medicine and a Master of Science in health policy and management from the Harvard School of Public Health. Jacquelyn frequently shares her insight and expertise with her medical peers through presentations and trainings. Her expertise as a Board-Certified Hematologist and Internist complements the clinical breadth of expertise already present.

EMPLOYMENT

2015 – Present Associate Medical Director

Change Healthcare, Augusta, Maine

- Provide clinical support to teams that develop and administer pharmacy benefits for Medicaid programs in several states, including conducting drug utilization reviews and staffing Pharmacy and Therapeutics committee meetings.
- For the state of Maine, provide oversight for management of DME and medical claims and contribute to development of policies such as coverage determination for genetic testing.

2016 – Present **Assistant Medical Director**
Community Health Options, Lewiston, Maine

- Provide medical oversight of utilization management and collaborate on development of clinical guidelines and quality assurance/compliance programs for the organization, a non-profit health insurance cooperative in Maine.

2016 – Present **Consultant**
New England Cancer Specialists, Maine

- Contracted to provide hematology/oncology care in an urgent care setting.
- Provide call coverage for the Hemophilia and Thrombosis Treatment Center.

PRIOR EMPLOYMENT

1985 – 1986	Consultant, Blue Cross Blue Shield, Massachusetts
1996 – 1997	Associate Medical Director, Coral Therapeutics, Inc. 1997-1998 Medical Director, Coral Therapeutics, Inc.
1998 – 2011	Consulting Medical Director, Coral Blood Services, Inc. 1998-2016 Physician Partner/Owner, New England Cancer Specialists
2015 – 2016	Consulting Physician, Martin's Point Health Care Plan

FACULTY APPOINTMENTS

1998 – 2009	Clinical Instructor, University of Vermont College of Medicine Clinical Instructor, Tufts University School of Medicine

HOSPITAL AND ADMINISTRATIVE APPOINTMENT

1985 – 1986	Teaching Assistant, Harvard School of Public Health, Statistical Methods for Health Policy and Management
1996 – 2004	Assistant Director, Maine Hemophilia Treatment Center
1998 – 1999	Transfusion Medicine Consultant, Maine Medical Center
1998 – 2007	Medical Director, Maine Medical Center Outpatient IV Therapy Room
2004 – 2008	Clinical Medical Director, Bone Marrow Transplant Program, Maine Medical Center
2004 – Present	Attending Physician, Maine Hemophilia Treatment Center Medical Director, Maine Medical Center Cancer Institute
2010 – Present	Medical Director, Gibson Pavilion Cancer Care Floor, Maine Medical Center
2012 – 2013	Service Line Physician Leader, Oncology Service Line, Maine Medical Center

EDUCATION

1990 **University of Vermont College of Medicine, Burlington, VT**
- Doctor of Medicine

1986 **Harvard School of Public Health, Boston, Massachusetts**
- M.S. Health Policy and Management

1983 **Smith College, Northhampton, Massachusetts**
- A.B. Economics

POSTGRADUATE TRAINING AND FELLOWSHIP APPOINTMENTS

1990 – 1993	Internal Medicine Residency, Maine Medical Center, Portland, ME 1993-1994 Chief Medical Resident, Maine Medical Center, Portland, ME
1994 – 1996	Hematology Fellowship, University of Washington, Seattle, WA 1995-1996 Transfusion Medicine Fellowship, Puget Sound Blood Center, Seattle, WA

ADDITIONAL TRAINING

2008	Harvard School of Public Health, Leadership Strategies for Evolving Health Care Executives, Boston, MA
2008 – 2009	MaineHealth, Physician Leadership Development Fellowship, Portland, ME
2009	Harvard School of Public Health, Intensive Seminar for New and Emerging Leaders. Boston, MA
2011	Maine Medical Center, Portland, ME, Clinical Microsystems Team Training

PROFESSIONAL LICENSES, CERTIFICATIONS AND MEMBERSHIPS

BOARD CERTIFICATION
- 1993 Internal Medicine
- 1997 Hematology
- 2003 Internal Medicine Recertification
- 2007 Hematology Recertification
- 2014 Internal Medicine Recertification

LICENSURE
- Maine
- Massachusetts [redacted]

COMMITTEE MEMBERSHIPS

1991 – 1994	Health and Public Policy Committee, Maine Chapter of the American College of Physicians
1991 – 1993	National Council of Associates, American College of Physicians, Steering Committee
1992 – 1993	American College of Physicians Access to Health Care Reform
1998 – 2004	Transfusion Committee, Maine Medical Center
1999 – 2002	Clinical Advisory Committee, Maine Medical Center
1999 – 2003	Medical Audit Committee, Maine Medical Center
2002 – 2004	Medical Executive Committee, Maine Medical Center
2002 – 2013	Pharmacy & Therapeutics Committee, Maine Medical Center
2007 – 2012	Performance Improvement Committee, Maine Medical Center
2007 – 2013	Chair, Maine Medical Center Oncology Steering Committee
2007 – 2009	Research Strategic Plan Steering Committee, Maine Medical Center
2008 – 2013	Technology Assessment Committee, Maine Medical Center
2008 – 2013	MaineHealth Oncology Leadership Team
2008 – 2013	Chiefs' Committee, Maine Medical Center
2008 – 2013	Leadership Team, Maine Medical Center
2009 – 2011	Co-Chair, Maine Health Oncology Quality Committee
2011 – 2013	MaineHealth Oncology Quality Committee
2011 – 2013	Clinical Applications Steering Committee EPIC Shared Health Record Implementation: MMC

PROFESSIONAL SOCIETIES

1990 – Present	American College of Physicians
1994 – Present	American Society of Hematology
1996 – 2006	American Society for Aphaeresis
1996 – 2012	American Association of Blood Banks
1998 – 2013	International Society for Hemostasis and Thrombosis
2006 – Present	American Society of Clinical Oncology (ASCO)
2007 – 2013	Association of Community Cancer Centers, Delegate

COMMUNITY SERVICE

2004 – 2007	Member, Board of Directors, Maine Cancer Foundation
2010 – 2015	Member, Board of Directors, United Way Greater Portland
2013 – 2016	Member, Board of Directors, Piper Shores Continuing Care Retirement Community (non-profit)
2013 – 2016	Chair, Memory Care Work Group, Piper Shores
2013 – 2014	Member, Strategic Planning Work Group, Piper Shores

CHERIEANN HARRISON

Operation Supervisor

SUMMARY OF EXPERIENCE

As the Operation Supervisor that manages the Rebate Medicaid Negotiations for Change Healthcare since 2017, I have had the opportunity to work with both a 'Pool' of States, and States that have opted to work as a 'Stand Alone'. My team annually solicits and guides our States through the Offer Acceptance process for Supplemental Rebate and Diabetic Medical Equipment. Additionally, States that utilize Change Healthcare's PDL services are provided Contracting and Pricing File management services through the Rebate Medicaid Negotiations team.

EMPLOYMENT

2017 – Present Operation Supervisor of Drug Rebate Negotiated Contracts
Change Healthcare, Augusta, Maine

- Management of Bid Cycle Solicitations
- Contract Management
- Pricing File Generation Oversite
- Portal/System Process Improvement for the Electronic Rebate Offer Management System (EROMS) and the Rebate Administration system (Rebate Admin)

2015 – 2017 Rebate Specialist III
Change Healthcare, Augusta, Maine

- Trainer
- Developed Operation Standards of Practice
- 340 B Management
- Dispute Lead
- Invoicing Lead

2015 – 2015 Rebate Specialist I
GHS Division of Change Healthcare, Augusta, Maine

- Dispute Resolution
- Retail Pharmacy Liaison
- Invoicing

2013 – 2014 Nationally Certified Pharmacy Technician/CSS
Coram Home Infusion Pharmacy, Falmouth, Maine

- Trainer
- Patient one to one agent to assist in reordering of medications
- Compound Specialist
- Chemotherapy Preparation/Compound Specialist

2008 – 2013 Nationally Certified Pharmacy Technician
Franklin Memorial Hospital, Farmington, Maine

- Compound Specialist
- Pyxis Management
- On Demand Prescription Fill

2007 – 2008 Nationally Certified Pharmacy Technician- Lead Technician
CVS Pharmacy, Woodbridge, Virginia

- Trainer
- Technician Management/Scheduling/Hiring/Development/Firing
- Responsible for Placement of Pharmacy Order
- Prescription Fill

2001 – 2008 Nationally Certified Pharmacy Technician- Lead Technician
Howard's Rexall Pharmacy, Farmington, Maine

- Prescription Fill
- Bubble Pak Management for local Assisted Living Facilities
- Compounding of Progesterone Capsules and Suppositories
- Compounding of Creams/Lotions, etc.

2000 – 2001 Pharmacy Technician
Kindred Pharmaceuticals, Norwood, Massachusetts

- Bubble Pak Preparation
- Prescription Fill
- Light Compounding Responsibilities

EDUCATION

2007 University of Maine at Farmington, Farmington, Maine

- Bachelor of Arts in Independent Study with concentration in Biology/Chemistry
- Officer of Financial Affairs for the UMF Student Senate 2006-2007
- UMF Student Senate Member 2005-2007
- UMF Senior Class Vice-President

CHRISTINE DEPROFIO

SMAC Program Support

SUMMARY OF EXPERIENCE

Mrs. Christine DeProfio joined the Change Healthcare team in 2006, hired to assist in the Medicare Part D program for the state of Maine. In this position she worked closely with Part D clients and pharmacists assisting in navigating the enrollment process and prescription drug coverage issues of the Medicare Part D prescription program, which can sometimes be a confusing process for clients. Christine's excellent customer service skills allowed her to guide clients and provide pharmacists with the information they needed in an effective and efficient manner. She was also responsible for reviewing and supporting reporting and analysis as it related to Part D. Her work in this position helped her to grow strong knowledge of policies and procedures, bringing a high level of quality and integrity to the Part D programs she worked with.

In 2010, Christine began working with the State Maximum Allowable Cost (SMAC) programs; researching and corresponding with stores to resolve their reimbursement issues. She is responsible for collecting records and verifying for completeness the fax disputes received from pharmacies. Christine supports the SMAC programs for all 9 of Change Healthcare's SMAC clients and has a strong focus on drug pricing strategies which are employed by state Medicaid programs. Her efforts effectively support Change Healthcare's strategies used for SMAC pricing for both generics and brands, helping our clients better manage their Medicaid program costs.

EMPLOYMENT

2010 – Present MAC Program Support/Reimbursement Specialist
Change Healthcare, Augusta, Maine

State Maximum Allowable Cost (SMAC) Experience
Actively involved in implementing and ongoing operations of the SMAC programs for 10 states including: Illinois, Maine, Minnesota, New Jersey, North Dakota, Ohio BWC, Vermont, West Virginia, and Wyoming.

In collaboration with the Change Healthcare SMAC team, Christine has helped state Medicaid programs better controls costs. For example, efforts in West Virginia have averaged savings of $4 million monthly. As our largest SMAC client, Illinois realizes an average of $25 million in savings per quarter. In addition, Christine's daily responsibilities include:

- Familiarity with drug pricing strategies for both generics and brands, including specialty drugs
- Utilize understanding of Change Healthcare's strategies used to design and operate SMAC programs in conjunction with FULs and CMS
- Development of new SMAC prices, revise old SMAC prices and perform all intermediate steps throughout the process
- Answer calls from pharmacies having pricing issues relating to SMAC
- Enter all dispute information into Excel spreadsheet
- Coordinate file transfers to and from states with pricing disputes

- Contact stores with resolutions
- Utilize database of information to track and record all acquisition survey information
- Enter all acquisition data for use in rebasing SMAC pricing
- Ensure SMAC programs are equipped with the tools to operate smoothly and effectively for all Change Healthcare clients

2006 – 2010 Medicare Part D Specialist
Change Healthcare, Augusta, Maine

- Answer member questions regarding enrollment and prescription coverage
- Assist pharmacies with drug coverage questions
- Learn policies and procedures for each PDP account to maintain accuracy of responses
- Review and support of reporting process and analysis relative to Part D
- Responsible for the quality and integrity of all Part D representation
- Apply policies and business rules relative to the Part D process
- Support roles dealing with all aspects of plan selection processes and customer service, requests for services

EDUCATION

2003 – 2005 Kennebec Valley Community College

- Associates Degree, Medical Office Administration
- Internship, Maine General Medical Center – ER Department

JOHN GROTTON, RPH

Senior Director, Medicaid Pharmacy Operations

SUMMARY OF EXPERIENCE

John joined the Change Healthcare team in 1997 and he is currently responsible for oversight of our Clinical and Account Management teams. He has overseen the design and implementation of nearly every one of the Medicaid PBS division's PBM clients including Illinois, Ohio, Utah, Wyoming, Iowa, Vermont and Maine. Most recently, he was instrumental in the development of the pharmacy point of sale (POS) for the State of Illinois in a software-as-a-service (SaaS) application. He has extensive experience with design, development, implementation, and operation of Medicaid pharmacy programs with particular expertise in PDL management, pricing, formulary management, claims processing, rebate and 340B policy. In addition to his experience at Change Healthcare, he has 20 years of experience in retail pharmacy.

John is a graduate of the College of Pharmacy at Northeastern University and is a licensed pharmacist in two states. He has worked as a district supervisor for two large retail pharmacy chains and as a pharmacy intern in a large metropolitan hospital. John is a past president of the Maine Board of Pharmacy and is a member of the Maine Pharmacy Association.

To our state clients, he brings his expertise with project coordination of health care reform program changes, drug rebate and related clinical pharmacy contract cost modeling, formulary and PDL development and maintenance. He has worked with our clients to provide analysis of pharmacoeconomic data for PDL decisions and he is an active part of the implementation team.

EMPLOYMENT

2004–Present Senior Director Medicaid PBM Services
Change Healthcare, Augusta, Maine

- Responsible for design, development, implementation and operation of Medicaid pharmacy programs including:
  - Formulary/PDL management, - covered products, preferred/ non-preferred status, rebate eligibility
  - Expertise in implementation of pricing methodologies including NADAC, AAC, AWP, WAC, 340B, SMAC
  - Expertise in Federal and State rebate policy
  - 340B – Extensive experience implementing 340B programs for hospitals and States
  - Claims processing – member of NCPDP bridge between pharmacy policy, DUR and claims processing
    - J-Code /Physician administered drugs– designed crosswalk to facilitate State rebate collections for physician administered drugs
  - DUR – Support DUR committees in multiple states, Liaison between DUR and claims processing edits
  - Product Development – Subject matter expert for design of PADSS system, POS system, PDL application, Formulary application and eREBS
  - SMAC – oversees generic pricing in 8 states
  - Manages a clinical staff of 11 direct reports

- Served as Member of the Drug Utilization Review Board for Maine's Medicaid Program (1996–2004).

1997–2004 Vice President of Operations
Change Healthcare, Augusta, Maine

- Responsible for assuring the needs of clients were met in an appropriate, effective, and cost-efficient manner
- Served a wide spectrum of clients including State and local agencies, pharmacies, various medical associations, HMOs, hospitals, and private corporations
- Assisted client organizations in the design, development, implementation, and administration of flexible, efficient data servicing solutions, using the most advanced technology available

1998–2004 Vice President
Community Pharmacies, LP, Augusta, Maine

- Co- Founder Community Pharmacy of Maine
- Oversaw the daily operations of 15 retail pharmacies located in various towns across Maine
- Responsible for the growth, development, and operation of stores
- Ensured compliance with all applicable State and federal regulations and statutes

1987–1997 Pharmacy Development Manager/ Pharmacy District Supervisor
Rite Aid Corporation, Dover, New Hampshire

- Pharmacy Development Manager (1995–1997):
  - Responsible for assisting District Manager in setting appropriate goals and in implementation of customer service plans
  - Advised District and Market Managers on issues relative to personnel productivity
  - Counseled and advised store pharmacists. Coordinated professional development and training for pharmacy personnel
- Pharmacy District Supervisor (1987–1995):
  - Supervised pharmacy operations in 26 stores across Maine
  - Responsible for all aspects of pharmacy administration, including hiring, firing, payroll, scheduling, inventory control, third party claims, and disciplinary actions

1977–1987 Pharmacy Manager / Staff Pharmacist
Laverdiere's Super Drug Store (no longer in operation)

- Supervised pharmacy operations in twenty-five stores located across Maine and New Hampshire
- Responsible for all aspects of daily operations
- Worked as pharmacist/manager for pharmacy operations in various Laverdiere's stores in Maine and New Hampshire

1973–1977 Intern
Peter Bent Brigham Hospital, Boston, Massachusetts

- Studied all aspects of hospital pharmacy operations; assisted staff pharmacist in carrying out daily duties

EDUCATION

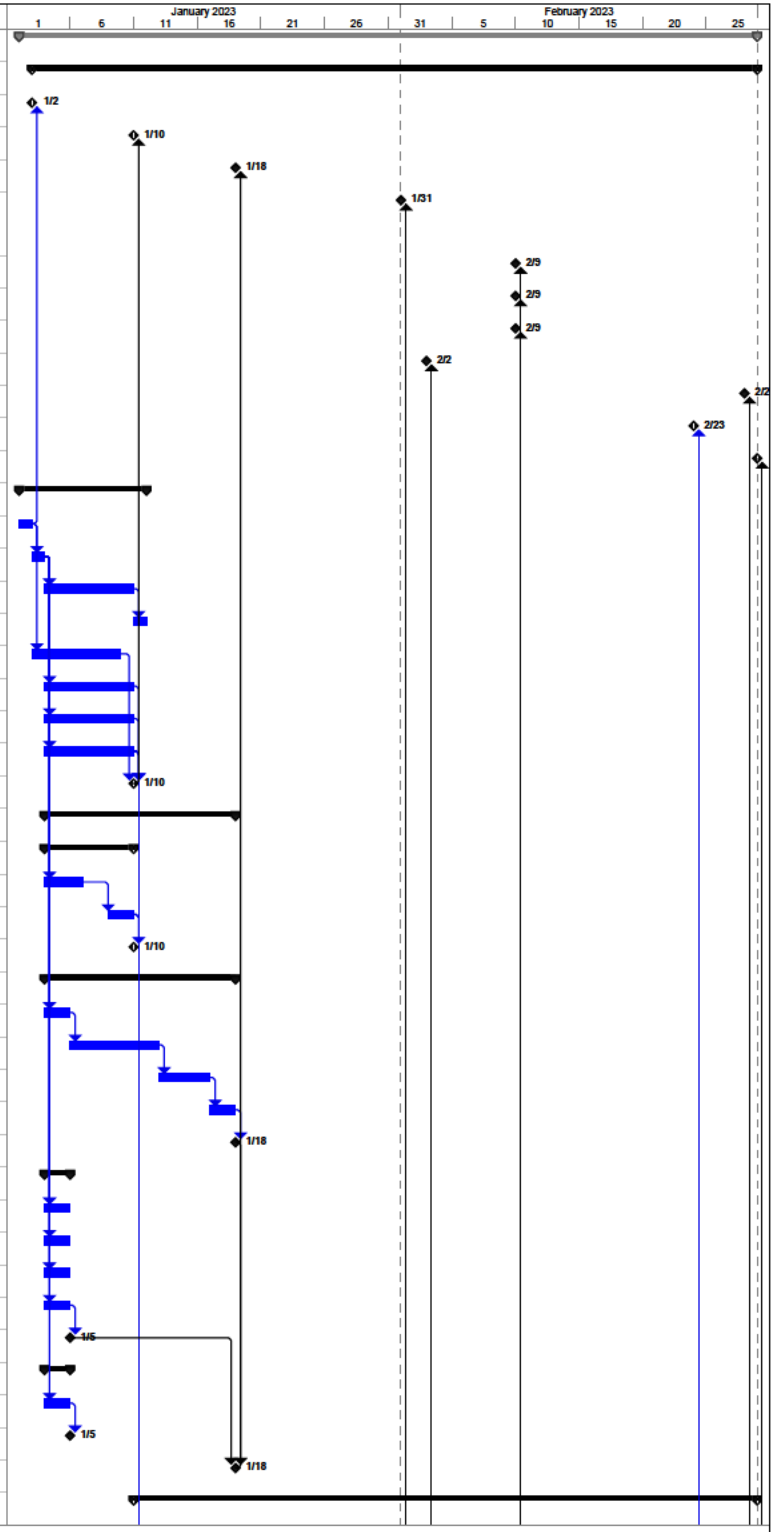
1972 – 1977 Northeastern University College of Pharmacy, Boston, Mass.

- B.S. Pharmacy, Cum Laude

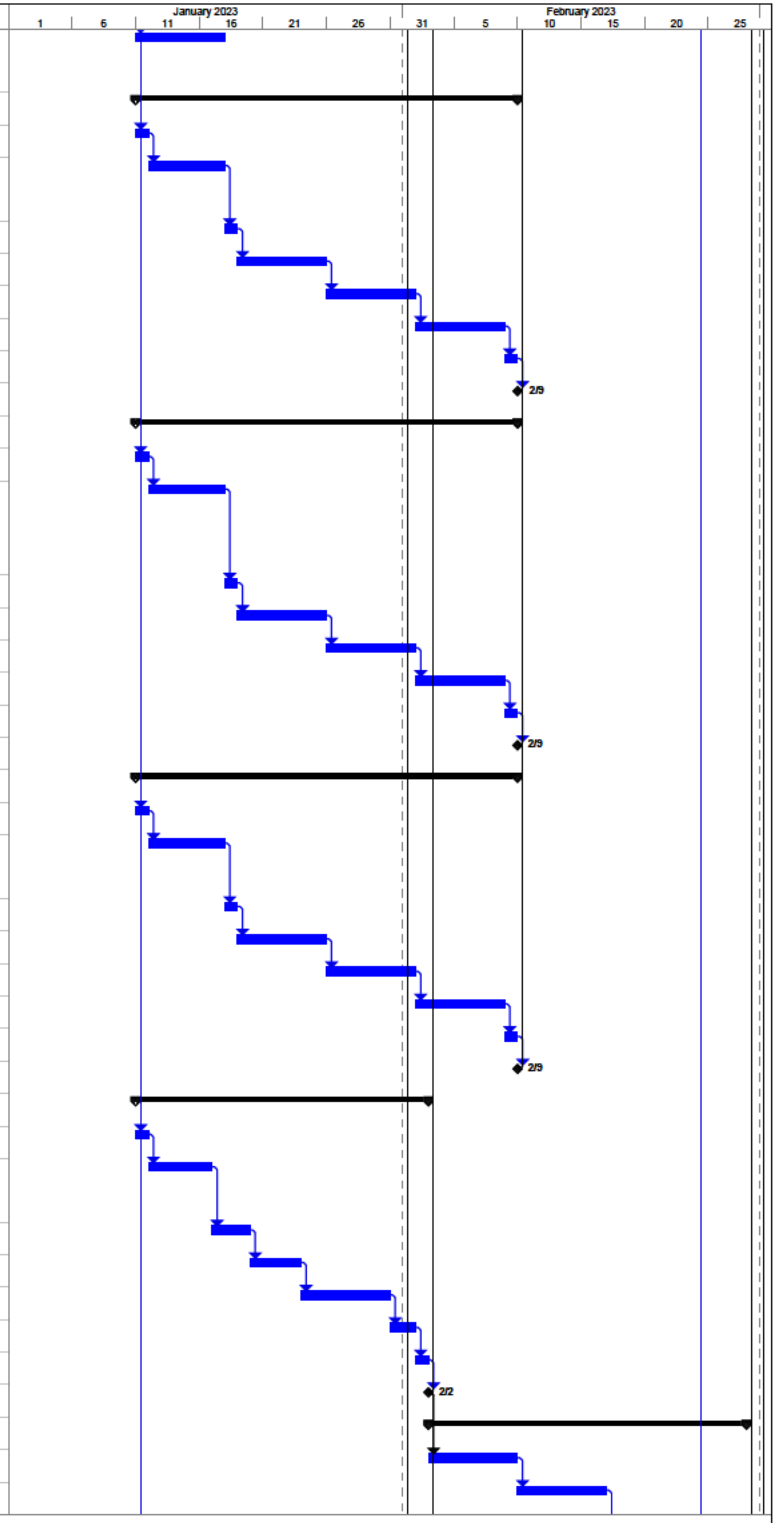
PROFESSIONAL LICENSES, CERTIFICATIONS AND MEMBERSHIPS

- Licensed Pharmacist in Maine and New Hampshire.
- Member, State of Maine Board of Pharmacy, 1995–2001
- President, Maine Board of Pharmacy, 1998-2001
- Member, State of Maine Drug Utilization Review Committee, 1996–2004
- Member, Maine Pharmacy Association
- Member, Maine Health Data Processing Center Board of Directors 2003–2004

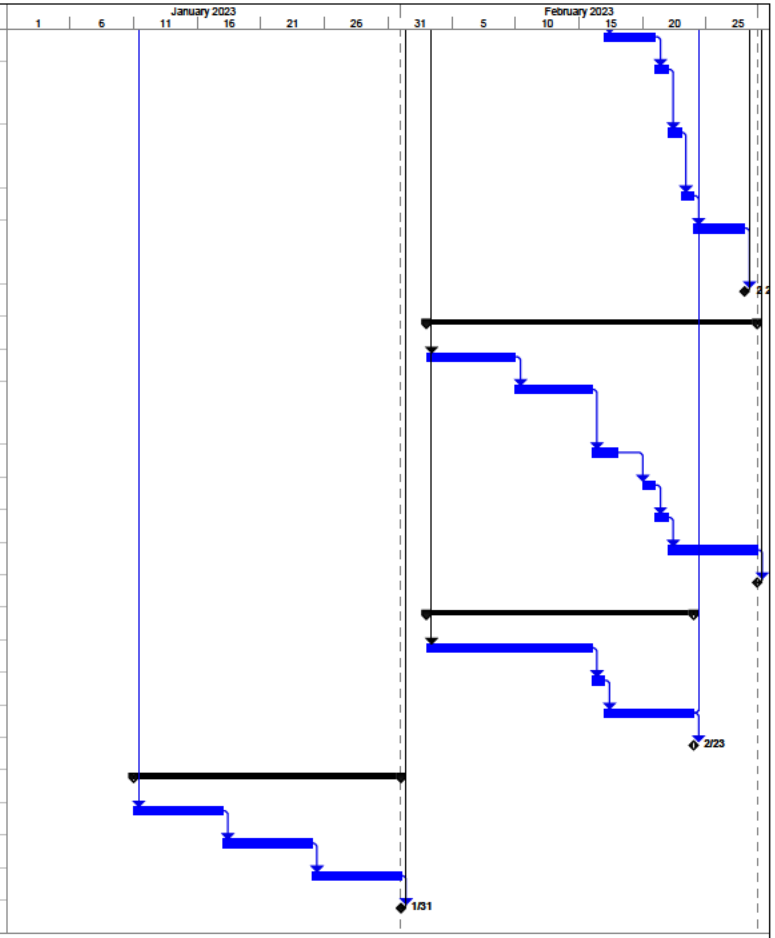
ID	Task Name	Duration	Start	Finish	Predecessors	Resource Title	Team
0	**WV SMAC PDL Program Review Project Plan**	**42 days**	**Mon 1/2/23**	**Tue 2/28/23**			
1	**Milestones**	**41 days**	**Mon 1/2/23**	**Tue 2/28/23**			
2	M: Critical Milestone 1: Contract Award	0 days	Mon 1/2/23	Mon 1/2/23	14		
3	M: Critical Milestone 2: Contract Activities Completed	0 days	Tue 1/10/23	Tue 1/10/23	22		
4	M: Critical Milestone 3: Project Initiation and Planning Completed	0 days	Wed 1/18/23	Wed 1/18/23	43		
5	M: Critical Milestone 4: Implementation of High Cost Physician Administered Drug List Complete	0 days	Tue 1/31/23	Tue 1/31/23	108		
6	M: Critical Milestone 5: PDL Review Complete	0 days	Thu 2/9/23	Thu 2/9/23	54		
7	M: Critical Milestone 6: Weekly Drug File Process Complete	0 days	Thu 2/9/23	Thu 2/9/23	63		
8	M: Critical Milestone 7: PPL Review Complete	0 days	Thu 2/9/23	Thu 2/9/23	72		
9	M: Critical Milestone 8: SMAC Review Complete	0 days	Thu 2/2/23	Thu 2/2/23	81		
10	M: Critical Milestone 9: P&T Review Complete	0 days	Mon 2/27/23	Mon 2/27/23	90		
11	M: Critical Milestone 10: Reporting Review Complete	0 days	Thu 2/23/23	Thu 2/23/23	102		
12	M: Critical Milestone 11: Supplemental Rebate Review Complete	0 days	Tue 2/28/23	Tue 2/28/23	98		
13	**Contract Activities**	**8 days**	**Mon 1/2/23**	**Wed 1/11/23**			
14	M: Contract Award	1 day	Mon 1/2/23	Mon 1/2/23			
15	Approval to Start Program Review from Client	1 day	Tue 1/3/23	Tue 1/3/23	14	State	State
16	Contract pre-terms agreed upon	5 days	Wed 1/4/23	Tue 1/10/23	15	Project Manager, State	CH, State
17	Final Contract Executed	1 day	Wed 1/11/23	Wed 1/11/23	16	Project Manager, State	CH, State
18	Confirm vendor registration status	5 days	Tue 1/3/23	Mon 1/9/23	14	State	State
19	Confirm proof of coverage of liability insurance for loss, damage, or injury	5 days	Wed 1/4/23	Tue 1/10/23	15	Project Manager	CH
20	Confirm good standing with the State Agency of Employment Programs	5 days	Wed 1/4/23	Tue 1/10/23	15	Project Manager, State	CH, State
21	Provide proof of licensure as requested	5 days	Wed 1/4/23	Tue 1/10/23	15	Project Manager	CH
22	M: Contract Activities Completed	0 days	Tue 1/10/23	Tue 1/10/23	21,20,19,18		
23	**Project Initiation and Planning**	**11 days**	**Wed 1/4/23**	**Wed 1/18/23**			
24	**Project Kick-Off**	**5 days**	**Wed 1/4/23**	**Tue 1/10/23**			
25	Prepare meeting materials including project plan, communication	3 days	Wed 1/4/23	Fri 1/6/23	15	Project Manager, Business Analyst	CH
26	Conduct a kick-off meeting	2 days	Mon 1/9/23	Tue 1/10/23	25	Project Manager, State	CH, State
27	M: Project Kick-Off Complete	0 days	Tue 1/10/23	Tue 1/10/23	26		
28	**Work Plan**	**11 days**	**Wed 1/4/23**	**Wed 1/18/23**			
29	Create Initial Work Plan	2 days	Wed 1/4/23	Thu 1/5/23	15	Project Manager	CH
30	State Review	5 days	Fri 1/6/23	Thu 1/12/23	29	State	State
31	Revise and Resubmit	2 days	Fri 1/13/23	Mon 1/16/23	30	Project Manager	CH
32	State Review and Approve Baseline Work Plan	2 days	Tue 1/17/23	Wed 1/18/23	31	State	State
33	M: Baseline Work Plan Complete	0 days	Wed 1/18/23	Wed 1/18/23	32		
34	**Project Tracking Logs (RAID)**	**2 days**	**Wed 1/4/23**	**Thu 1/5/23**			
35	Establish Risk Log	2 days	Wed 1/4/23	Thu 1/5/23	15	Project Manager	CH
36	Establish Action Item Log	2 days	Wed 1/4/23	Thu 1/5/23	15	Project Manager	CH
37	Establish Issue Log	2 days	Wed 1/4/23	Thu 1/5/23	15	Project Manager	CH
38	Establish Decision Log	2 days	Wed 1/4/23	Thu 1/5/23	15	Project Manager	CH
39	M: Project Tracking Logs Set Up Complete	0 days	Thu 1/5/23	Thu 1/5/23	38		
40	**Establish Weekly Status Meetings**	**2 days**	**Wed 1/4/23**	**Thu 1/5/23**			
41	Schedule Weekly Status Meetings	2 days	Wed 1/4/23	Thu 1/5/23	15	Project Manager	CH
42	M: Establish weekly status meetings complete	0 days	Thu 1/5/23	Thu 1/5/23	41		
43	M: Project Initiation and Planning Complete	0 days	Wed 1/18/23	Wed 1/18/23	39,33		
44	**WV PDL/PPL/SMAC Program Review**	**35 days**	**Wed 1/11/23**	**Tue 2/28/23**			



ID	Task Name	Duration	Start	Finish	Predecessors	Resource Title	Team
45	Submit weekly implementation status reports (recurring throughout Implementation Phase)	5 days	Wed 1/11/23	Tue 1/17/23	26	Project Manager	CH
46	**Preferred Drug List (PDL)**	**22 days**	**Wed 1/11/23**	**Thu 2/9/23**			
47	Meet with fiscal agent to review file requirements for PDL	1 day	Wed 1/11/23	Wed 1/11/23	21	Project Manager, State	CH, State
48	Review formatting, maintenance needs, file formats, and schedule for all PDL documents, including those publicly posted on website	4 days	Thu 1/12/23	Tue 1/17/23	47	Project Manager, State	CH, State
49	Submit PDL for approval	1 day	Wed 1/18/23	Wed 1/18/23	48	Project Manager	CH
50	State approves PDL	5 days	Thu 1/19/23	Wed 1/25/23	49	State	State
51	State/fiscal agent approves updated file feed/layout	5 days	Thu 1/26/23	Wed 2/1/23	50	State	State
52	Review newsletter layout and initial content	5 days	Thu 2/2/23	Wed 2/8/23	51	State	State
53	State approves newsletter	1 day	Thu 2/9/23	Thu 2/9/23	52	State	State
54	M: PDL Review Complete	0 days	Thu 2/9/23	Thu 2/9/23	53		
55	**Weekly Drug File Process**	**22 days**	**Wed 1/11/23**	**Thu 2/9/23**			
56	Meet with fiscal agent to review requirements for Weekly Drug File Process	1 day	Wed 1/11/23	Wed 1/11/23	21	Project Manager, State	CH, State
57	Review formatting, maintenance needs, file formats, and schedule for all Weekly Drug File Process documents, including those publicly posted on website	4 days	Thu 1/12/23	Tue 1/17/23	56	Project Manager, State	CH, State
58	Submit Weekly Drug File Process for approval	1 day	Wed 1/18/23	Wed 1/18/23	57	Project Manager	CH
59	State approves Weekly Drug File Process	5 days	Thu 1/19/23	Wed 1/25/23	58	State	State
60	State/fiscal agent approves updated file feed/layout	5 days	Thu 1/26/23	Wed 2/1/23	59	State	State
61	Review newsletter layout and initial content	5 days	Thu 2/2/23	Wed 2/8/23	60	State	State
62	State approves newsletter	1 day	Thu 2/9/23	Thu 2/9/23	61	State	State
63	M: Weekly Drug File Process Review Complete	0 days	Thu 2/9/23	Thu 2/9/23	62		
64	**Preferred Product List (PPL)**	**22 days**	**Wed 1/11/23**	**Thu 2/9/23**			
65	Meet with fiscal agent to review requirements for PPL	1 day	Wed 1/11/23	Wed 1/11/23	21	Project Manager, State	CH, State
66	Review formatting, maintenance needs, file formats, and schedule for all PPL documents, including those publicly posted on website	4 days	Thu 1/12/23	Tue 1/17/23	65	Project Manager, State	CH, State
67	Submit PPL for approval	1 day	Wed 1/18/23	Wed 1/18/23	66	Project Manager	CH
68	State approves PPL	5 days	Thu 1/19/23	Wed 1/25/23	67	State	State
69	State/fiscal agent approves updated file feed/layout	5 days	Thu 1/26/23	Wed 2/1/23	68	State	State
70	Review newsletter layout and initial content	5 days	Thu 2/2/23	Wed 2/8/23	69	State	State
71	State approves newsletter	1 day	Thu 2/9/23	Thu 2/9/23	70	State	State
72	M: PPL Review Complete	0 days	Thu 2/9/23	Thu 2/9/23	71		
73	**State Maximum Allowable Cost (SMAC) Program**	**17 days**	**Wed 1/11/23**	**Thu 2/2/23**			
74	Meet with fiscal agent to review file requirements for SMAC	1 day	Wed 1/11/23	Wed 1/11/23	21	Project Manager, State	CH, State
75	Review formatting, maintenance needs, file formats, and schedule for all SMAC documents, including those publicly posted on website	3 days	Thu 1/12/23	Mon 1/16/23	74	Project Manager, State	CH, State
76	Review current Help Desk operations	3 days	Tue 1/17/23	Thu 1/19/23	75	Project Manager, State	CH, State
77	Submit SMAC Program for approval	2 days	Fri 1/20/23	Mon 1/23/23	76	Project Manager	CH
78	State/vendor approves updated file feed/layout	5 days	Tue 1/24/23	Mon 1/30/23	77	State	State
79	Documentation and system review finalized	2 days	Tue 1/31/23	Wed 2/1/23	78	Project Manager, State	CH, State
80	State approves final documentation/layouts	1 day	Thu 2/2/23	Thu 2/2/23	79	State	State
81	M: SMAC Review Complete	0 days	Thu 2/2/23	Thu 2/2/23	80		
82	**Pharmaceutical & Therapeutics Committee**	**17 days**	**Fri 2/3/23**	**Mon 2/27/23**			
83	Review therapeutic class review/monograph/new drug review templates	5 days	Fri 2/3/23	Thu 2/9/23	81	Project Manager, State	CH, State
84	State approves P&T templates	5 days	Fri 2/10/23	Thu 2/16/23	83	State	State



ID	Task Name	Duration	Start	Finish	Predecessors	Resource Title	Team
85	Plan P&T meeting	2 days	Fri 2/17/23	Mon 2/20/23	84	Project Manager, State	CH, State
86	Provide financial information for the P & T Committee for each therapeutic class at least annually	1 day	Tue 2/21/23	Tue 2/21/23	85	Project Manager	CH
87	Provide financial information for the P & T Committee for each new drugs as they are reviewed by the P & T Committee at least quarterly	1 day	Wed 2/22/23	Wed 2/22/23	86	Project Manager	CH
88	Confirm no additional monograph updates are needed	1 day	Thu 2/23/23	Thu 2/23/23	87	State	State
89	Review new drugs or drug formulations using a schedule agreed to by the Vendor and BMS, at a minimum quarterly.	2 days	Fri 2/24/23	Mon 2/27/23	88	Project Manager, State	CH, State
90	M: P&T Review Complete	0 days	Mon 2/27/23	Mon 2/27/23	89		
91	**Supplemental Rebate Program**	**18 days**	**Fri 2/3/23**	**Tue 2/28/23**			
92	Review SR/OBRA rebate collection with the State and fiscal agent	5 days	Fri 2/3/23	Thu 2/9/23	81	Project Manager, State	CH, State
93	Review formatting, SR agreements, maintenance needs, file formats, and schedule for all SR documents, including those publicly posted on website	4 days	Fri 2/10/23	Wed 2/15/23	92	Project Manager, State	CH, State
94	GHS review of layout & signoff	2 days	Thu 2/16/23	Fri 2/17/23	93	Project Manager, State	CH, State
95	Documentation and system review finalized	1 day	Mon 2/20/23	Mon 2/20/23	94	Project Manager, State	CH, State
96	Submit Supplemental Rebate Program for Approval	1 day	Tue 2/21/23	Tue 2/21/23	95	Project Manager	CH
97	State and Fiscal Agent approves final documentation and/or file layouts	5 days	Wed 2/22/23	Tue 2/28/23	96	State	State
98	M: Supplemental Rebate Review Complete	0 days	Tue 2/28/23	Tue 2/28/23	97		
99	**Reporting**	**15 days**	**Fri 2/3/23**	**Thu 2/23/23**			
100	Review current reports	9 days	Fri 2/3/23	Wed 2/15/23	81	Project Manager, State	CH, State
101	Submit Report Package for Approval	1 day	Thu 2/16/23	Thu 2/16/23	100	Project Manager	CH
102	State approves reports	5 days	Fri 2/17/23	Thu 2/23/23	101	State	State
103	M: Reporting Review Complete	0 days	Thu 2/23/23	Thu 2/23/23	102		
104	**Implement High Cost Physician Administered Drug List**	**15 days**	**Wed 1/11/23**	**Tue 1/31/23**			
105	Joint review of program requirements	5 days	Wed 1/11/23	Tue 1/17/23	21	Project Manager, State	CH, State
106	Establish operational strategy to support program	5 days	Wed 1/18/23	Tue 1/24/23	105	Project Manager, State	CH, State
107	Implement HCPADL program	5 days	Wed 1/25/23	Tue 1/31/23	106	Project Manager	CH
108	M: Implementation of High Cost Physician Administered Drug List Complete	0 days	Tue 1/31/23	Tue 1/31/23	107		



THERAPEUTIC CLASS REVIEW

OCTOBER 27, 2020

[Last Comprehensive Class Literature Review: February 1, 2019]

[Last Review Update: April 23, 2020]

HEPATITIS C TREATMENTS

This publication is a result of the collaboration of the Change Healthcare Clinical Workgroup and represents the opinion of these authors based on a review of the literature available at the time it was written. It is intended for the sole purpose of providing information to committee members in order to compare medications within a specified subset of clinical parameters. It is not intended to provide specific clinical advice for any condition, or to be an exhaustive review of all potential aspects of pharmacotherapies for any given condition. Medical evidence is rapidly changing, and no representation is made regarding the use of this material beyond the stated purpose. The literature for this review was last searched through the date listed above. Please note that it may take time for published articles to be available via medical literature search engines.

SYNOPSIS[1-2, 4, 6, 18, 27, 230]

Hepatic C virus (HCV) accounts for the majority of cases of cirrhosis and hepatocellular carcinoma, is the leading indication for liver transplants, and is a significant cause of hepatic morbidity and mortality. It is estimated that about 2.4 million persons in the US have chronic HCV infection[164], and that this number is upwards of 71 million worldwide.[264] According to the 2017 WHO Global Hepatitis Report, most hepatitis deaths were due to chronic liver disease (720,000 due to cirrhosis) and liver cancer (470,000 due to hepatocellular carcinoma) in 2015.[286] Of every 100 persons infected, approximately 1-5 will die from the consequences of chronic infection (i.e. liver cancer or cirrhosis).[164] The US CDC now recommends one-time hepatitis C testing of all adults (18 years and older) and all pregnant women during every pregnancy. The CDC continues to recommend people with risk factors, including people who inject drugs, be tested regularly.[351]

Hepatitis C is a virus that causes liver disease and inflammation of the liver. There are at least six major genotypes of hepatitis C virus that have been identified. The most common genotype found in the United States is genotype 1. The primary transmission of hepatitis C infection is through large or repeated percutaneous exposures to infectious blood, such as intravenous drug use, receipt of donated blood, blood products, and organs, needlestick injuries in the healthcare settings, or birth from an HCV-infected mother.[164] With the introduction of routine blood screening for HCV antibody in 1991, transfusion-related hepatitis C has virtually disappeared. In middle and high-income countries, most HCV infections occur among people who use nonsterile equipment to inject drugs and contaminated drug solutions. Of the estimated 16 million people in 148 countries who actively inject drugs, 10 million have serological evidence of HCV infection.[230]

It is difficult to differentiate hepatitis C from other viral hepatitis infections based on clinical presentation alone. Patients typically present with a chief complaint of fatigue, fever, dark urine, clay-colored stool, loss of appetite, abdominal pain, nausea/vomiting, or joint pain. Jaundice may also be a symptom. Although patients with this disease may be asymptomatic, the majority of patients with acute hepatitis C progress to chronic infection. It is estimated that approximately 55-85% of cases of HCV become chronic[164], and the risk of liver cirrhosis is between 15-30% within 20 years.[264]

Interferon α is a host protein that is made in response to viral infections and has natural antiviral activity. Initially, recombinant forms were produced (alfa-2a, alfa-2b). These forms were then replaced by pegylated interferon, which is an alpha interferon that has been chemically modified by the addition of a large inert molecule of polyethylene glycol that alters the uptake, distribution and excretion of interferon. This chemical alteration prolongs the half-life of the drug, allowing it to be administered weekly, thus producing a constant level of the drug, as opposed to the varying levels found with the non-pegylated versions of this protein. [18]

Prior to 2011, treatment for chronic hepatitis C (CHC) had relied on prolonged courses of interferon and ribavirin, often 24-48 weeks in length, which was poorly tolerated and resulted in resolution of the infection in 40-50% of those treated. In 2011, telaprevir (Incivek®) and boceprevir (Victrelis®) were approved for treatment of HCV in both treatment naïve and non-responders. Both being protease inhibitors, they represented a new mechanism of action in the armamentarium of medications to treat hepatitis C; although, they were only able to be used in combination with interferon and ribavirin. Treatment courses in

combination with interferon lasted at least 24 weeks for some and remained poorly tolerated, but with improved results. Even with greater efficacy, they had high treatment failure rates.

At the end of 2013, a new treatment approach that did not require co-administration with pegylated interferon in all cases was FDA-approved. Sofosbuvir (Sovaldi®), the first nucleotide analog NS5B polymerase inhibitor was approved for use in certain genotypes in combination with ribavirin without the need for interferon. In the last several years, additional combination products have been FDA approved that have not only expanded the interferon-free treatment options, but also are pangenotypic.

While these medications are safe and highly effective in most patients, the number of patients in need of treatment as well as the cost of the medications is a significant concern. In low income areas of the world, access to these medications and needed medical care is a significant barrier.[265] In addition, despite the overall very high efficacy of the new directing acting antivirals (DAAs), there is still a small percentage of patients that experience virologic failure or relapse, and it is especially more common in cirrhotic patients, as well as in those with more difficult to treat genotypes. More and more research is being conducted with patient-specific HCV pharmacogenomic analyses, especially in those who fail therapy looking at baseline polymorphisms/substitutions and resistance-associated substitutions that potentially correspond to treatment-failure. The hope is being able to tailor patients to certain medications based upon the results of the HCV genotype analysis to prevent virologic failures in the future.[263]

This clinical area has been rapidly changing and fortunately, a well-respected, evidence-based guideline has been promulgated jointly by the Infectious Disease Society of America (IDSA) and the American Association for the Study of Liver Disease (AASLD) and is updated frequently.[101]

Vertex Pharmaceuticals decided to discontinue the sales and distribution of their product telaprevir (Incivek®) at the end of October 2014, and this product was removed from this class review. In addition, in January 2015, Merck, the manufacturer of boceprevir (Victrelis®), disseminated a letter indicating that it was voluntarily discontinuing the manufacturing and distribution of Victrelis® by December 2015 in the US. Per the letter, this was a business decision by the company and not due to any safety or efficacy findings of the product. This product has also been removed from this review. Finally, Kadmon Pharmaceuticals discontinued interferon alfacon-1 (Infergen®), and this product was likewise removed.

The single agent medications in this therapeutic class review include peginterferon alfa-2a (Pegasys®), peginterferon alfa-2b (Peg-Intron®), ribavirin (Ribasphere®), and sofosbuvir (Sovaldi®). Copegus® (ribavirin) is no longer rebatable and thus has been removed from the review. Olysio® was discontinued by the manufacturer as of 5/25/2018. The Moderiba® formulation of ribavirin was discontinued on 07/02/2018. Rebetol® (ribavirin) is non rebatable. Daklinza® (daclatasvir) is listed as an inactive NDC and is no longer rebatable. These treatments have been removed from the review.

The fixed-dose combination products included in this therapeutic class review include: elbasvir/grazoprevir (Zepatier®); glecaprevir/pibrentasvir (Mavyret), ledipasvir/sofosbuvir (Harvoni®), ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira® pak), sofosbuvir/velpatasvir/voxilaprevir (Vosevi®), and velpatasvir/sofosbuvir (Epclusa®). Generic versions of ledipasvir/sofosbuvir and velpatasvir/sofosbuvir are now also available. Obmbitasvir/paritaprevir/ritonavir (Technivie®) and ombitasvir/paritaprevir/ritonavir/dasabuvir extended-release tablets (Viekira® XR) have been discontinued

by the manufacturer. Furthermore, both are currently non-rebatable and thus will be removed from the class review. There is no generic available for either of these products.

FDA APPROVED INDICATIONS[1-2, 4-6, 9, 26, 33-34, 98-100, 124, 158-160, 165, 193-194, 233, 254]

All medications in this therapeutic class are indicated for chronic hepatitis C (CHC) virus infection in those with compensated liver disease. Baseline hepatic laboratory and clinical parameters should be assessed prior to initiation of therapy. Further details are listed in the tables below.

Drug	peginterferon alfa-2a (Pegasys®)	peginterferon alfa-2b (Peg-Intron®)
Monotherapy only for CHC with compensated liver disease if contraindications or significant intolerance to other Hep C antivirals	X	
Monotherapy only for CHC with compensated liver disease if contraindications or significant intolerance of Rebetol® and is indicated for use only in previously untreated adults[1]		X
As part of combo regimen w/other Hep C antiviral drugs, for treatment of CHC w/compensated liver disease- adults	X	X
In combo w/ribavirin for pediatric patients ≥5 years with CHC and compensated liver disease	X	
In combo w/Rebetol® & approved Hep C virus NS3/4A PI[2] for adults with HCV genotype 1[3]		X
In combo w/Rebetol® with genotypes other than 1, pediatrics (3-17yrs), or w/genotype 1 infection where use of an HCV NS3/4A PI is not warranted per tolerability, contraindications, or other clinical factors[3]		X
Alone or in combo w/ribavirin without other HCV antiviral drugs is not recommended for treatment with CHC who previously failed therapy with an interferon-alfa	X	
Not recommended for treatment of patients with CHC who have had solid organ transplantion	X	
Treatment of Chronic Hepatitis B	X	

[1] Combination therapy provides substantially better response rates than monotherapy
[2] PI- protease inhibitor
[3] With compensated liver disease

The following table includes additional information regarding the non-interferon products in this class.

Additional Criteria with oral Antiviral Drugs	E/G	G/P [11]	L/S	O/P/R with d	ribavirin (various)	SOF	S/V/V	V/S
Must not be used as monotherapy					X	X		
Chronic HCV genotypes 1 or 4 infection w/or without ribavirin	X							
Chronic HCV w/genotype 1b without cirrhosis or w/compensated cirrhosis OR genotype 1a without cirrhosis or with compensated cirrhosis in combination w/ribavirin				X				
In HCV genotype 1, 2, 3, or 4 infections and those with HCV/HIV-1 co-infection						X		
Chronic HCV infection without cirrhosis or with compensated cirrhosis with genotype 1a or 3 & previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor							X[8]	
Use as part of combination antiviral treatment regimen with peginterferon alfa & ribavirin in HCV genotype 1 or 4						X		
Use as part of combination antiviral treatment regimen with ribavirin in HCV genotype 2 or 3						X[2]		
In combination with ribavirin to prevent post-transplant HCV reinfection up to 48W or until time of liver transplant						X		
Safety/efficacy of use >48 weeks[S] or 1 year[R] not established					X			
Patient with certain characteristics less likely to benefit from re-treatment after failing course of therapy[3]					X			
Indication based on undetectable HCV-RNA after 24-28W, on HCV genotype, & maintaining SVR 24W after last dose					X[S]			
Indication based on some w/histologic evidence of cirrhosis & some w/stable HIV disease & CD4 count >100cells/mm[4]					X[S]			
Safety/efficacy not established in liver/other organ transplant recipients or decompensated liver disease					X[S]			
Not recommended in patients w/decompensated liver disease				X				
Safety/efficacy not established in previous non-responders to interferon therapy					X			

Additional Criteria with oral Antiviral Drugs	E/G	G/P [11]	L/S	O/P/R with d	ribavirin (various)	SOF	S/V/V	V/S
Genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis			X[10]					
Chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection		X[9]					X[7]	X[6, 12]
Patients ≥ 12 years old weighing at least 45kg with HCV genotype 1 who previously have been treated with a regimen containing an HCV NS5A inhibitor or NS3/4A protease inhibitor but not both		X						
Patients 3 Years of Age and Older with Genotype 2 or 3 HCV in combination with ribavirin						X		

e/g- elbasvir/grazoprevir (Zepatier®); g/p-glecaprevir/pibrentasvir (Mayvret®); l/s- ledipasvir/sofosbuvir (Harvoni®); o/p/r with d- ombitasvir/paritaprevir/ritonavir co-packaged with dasabuvir (Viekira® pak); SOF-sofosbuvir (Solvadi®); s/v/v- sofosbuvir/velpatasvir/ voxilaprevir (Vosevi®); v/s- velpatasvir/sofosbuvir (Epclusa)® [R] Rebetol® use w/interferon alfa-2b. [S]Ribasphere® use w/interferon alfa-2b .

[2] Sovaldi® has also been studied in combination with ribavirin only for the treatment of patients with CHC co-infected with HIV-1 with genotype 1, 2 or 3. Per the prescribing information, the treatment decision for use in genotype 1 with Sovaldi® in combination with only ribavirin are for those ineligible to receive interferon-based regimens and should be guided by an assessment of the potential benefits and risks for the individual patient.

[3] Previous non-response, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, genotype 1 infection

[4] Including those with compensated cirrhosis

[6] Without cirrhosis or with compensated cirrhosis OR with decompensated cirrhosis for use in combination w/ribavirin

[7] Without cirrhosis or with compensated cirrhosis & have been previously treated with an HCV regimen containing an NS5A inhibitor

[8] Additional benefit of Vosevi® over sofosbuvir/velpatasvir not shown with genotype 1b, 2, 4, 5, or 6 infection previously treated w/sofosbuvir without an NS5A inhibitor

[9] Without cirrhosis or with compensated cirrhosis (Child Pugh A) in patients 12 ≥ years old weighing at least 45kg.

[10] Adults and pediatric patients 3 years of age and older including GT 1 or 4 who are liver transplant recipients without cirrhosis or with compensated cirrhosis, for use in combination with ribavirin; For GT 1 with decompensated cirrhosis with ribavirin

[11] Also recommended for 12 weeks in adults/pediatric patients ≥12 years or weighing ≥45kg who are liver or kidney transplant recipients

[12] Adult and pediatric patients 6 years of age and older or weighing at least 17 kg

DOSAGE FORMS, DOSE, MANUFACTURER[1-2,4-6,9,26,33-34,98-100,124,158-160,165,193-194, 233, 254]

The specific dosages vary significantly by product and indication.

Drug	Dosage form	Manufacturer
peginterferon alfa-2a (Pegasys®)	Vial for Injection: 180mcg/ml Prefilled syringe: 180mcg/0.5ml	Genentech
peginterferon alfa-2b (PegIntron®)	Vial for injection per 0.5ml: 50mcg	Merck Sharp & Dohme Corp.
ribavirin	Capsules: 200mg	Various generic manufacturers
ribavirin (Ribasphere Ribapak®)	Tablets (2-Pak): 600mg pak (200mg & 400mg tab) 800mg pak (2-400mg tabs) 1000mg pak (400mg & 600mg tab) 1200mg pak (2-600mg tab)	Kadmon
ribavirin (Ribasphere®)	Tablets: 200mg, 600mg Capsules: 200mg	Various generic manufacturers (Kadmon)
sofosbuvir (Sovaldi®)	Tablets: 200mg, 400mg	Gilead Sciences
Combination Products		
elbasvir/grazoprevir[1] (Zepatier®)	Tablets: 50mg/100mg	Merck
glecaprevir/pibrentasvir (Mavyret®)	Tablets: 100mg/40mg	Abbvie
ledipasvir/sofosbuvir (Harvoni®)	Tablets: 45mg/200mg, 90mg/400mg	One generic manufacturer (Gilead Sciences)
ombitasvir/paritaprevir/ritonavir with dasabuvir (Viekira® pak)	Fixed-dose tab co-packaged w/dasabuvir: 12.5mg/75mg/50mg co-packaged w/250mg dasabuvir tablets	Abbvie
sofosbuvir/velpatasvir/voxilaprevir (Vosevi®)	Tablets: 400mg/100mg/100mg	Gilead Sciences
velpatasvir/sofosbuvir (Epclusa®)	Tablets: 100mg/400mg	One generic manufacturer (Gilead Sciences)

[1] It is recommended to test patients with genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms prior to starting treatment with Zepatier® to determine dosage regimen and duration

PHARMACOLOLOGY[1-2, 4-6, 9, 26, 33-34, 98-100, 124, 158-160, 165, 193-194, 233, 254]

Interferons:

All interferon products are inducers of the innate antiviral immune response.

Peginterferon alfa-2b (Peg-Intron®) increases the levels of effector proteins, such as serum neopterin and 2'5' oligo adenylate synthetase, raises body temperature, and causes reversible decreases in leukocyte and platelet counts. It binds to and activates the human type 1 interferon receptor and is thought to have pleiotropic biological effects in the body.

Peginterferon alfa-2a (Pegasys®) stimulates the production of effector proteins, such as serum neopterin and 2'5' oligo adenylate synthetase. It binds to the human type 1 interferon receptor leading to receptor dimerization. It is also thought to have pleiotropic biological effects in the body.

Others

Protease inhibitors target the HCV NS3/4A protease, which is needed for viral replication. They are effective in genotype 1.

Sofosbuvir (Sovaldi®, Epclusa®) is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is needed for viral replication. It is a nucleotide prodrug that undergoes metabolism and is then incorporated into HCV RNA, acting as a chain terminator. It is effective in genotypes 1, 2, 3, and 4.

The exact mechanism of ribavirin is not fully known; however, it does have direct antiviral activity against several RNA viruses. Ribavirin is an antiviral agent.

Harvoni® is the fixed-dose combination product that contains both sofosbuvir and ledipasvir. Ledipasvir is an HCV NS5A inhibitor, which is required for viral replication.

Viekira® pak is a combination of ombitasvir (a HCV NS5A inhibitor), paritaprevir (an HCV NS3/4A protease inhibitor), and ritonavir (a CYP3A inhibitor). Ritonavir is not an active agent against HCV, but rather is a potent inhibitor that increases peak and trough levels of paritaprevir, resulting in greater drug exposure. Viekira® pak is co-packaged with dasabuvir. Dasabuvir is an HCV non-nucleoside NS5B palm polymerase inhibitor.

Zepatier® is a fixed-dose combination of elbasvir (HCV NS5A inhibitor) and grazoprevir (HCV NS3/4A protease inhibitor).

Vosevi® is a fixed-dose combination product containing velpatasvir (HCV NS5A inhibitor), sofosbuvir (see above), and voxilaprevir (an NS3/4A protease inhibitor).

Mavyret® contains in a fixed-dose combination an HCV NS3/4A protease inhibitor, glecaprevir, and a NS5A protease inhibitor, pibrentasvir.

Epclusa® is a fixed-dose combination containing velpatasvir (HCV NS5A inhibitor) and sofosbuvir (see above).

PHARMACOKINETICS[1-2, 4-6, 9, 26, 33-34, 98-100, 124, 158-160, 165, 193-194, 233, 254]

Each of the interferon products used to treat hepatitis C virus have a long elimination half-life allowing for three times/per week dosing (interferon) or once-weekly injections (peginterferon). Little data is available regarding the specific metabolic routes of these products except for ribavirin.

Drug	Time to Peak Concentration	Half-life	Excretion	Other
peginterferon alfa-2a (Pegasys®)	72-96 hrs	84-353 hrs [a]	Renal	Steady-state 5-8 weeks of once weekly dosing
peginterferon alfa-2b (Peg-Intron®)	15 – 44 hrs	22-60 hrs [a]	Renal: 30%	
ribavirin (various)	2 hrs	170-298 hrs [a]	Renal: 61% Fecal: 12%	AUC/C_{max} of tabs ↑ 42%/66% with high-fat meal vs 70%/70% with caps Steady state at 4 weeks
sofosbuvir (Sovaldi®)	S: 0.5-2 hrs PM: 2-4 hrs	S: 0.4 hrs PM: 27 hrs	Renal: 80% Fecal: 14% Expired air: 2.5%	High fat meal does NOT affect drug concentration Primary metabolite: GS-331007
Combination Products				
elbasvir/grazoprevir (Zepatier®)	E: 3-6 hr G: 0.5-3 hr	E: 24 hrs G: 31 hrs	E: >90% feces G: >90% feces	Can be taken without regards to food
glecaprevir/ pibrentasvir (Mavyret®)	G: 5 hrs P: 5 hrs	G: 6 hrs P: 13 hrs	G: 92% F/<1% R P: 97% F/ 0% R	Take with food
ledipasvir/sofosbuvir (Harvoni®)	L: 4-4.5hr S: 0.8-1 hr PM: 3.5-4 hrs	L: 47 hrs S: 0.5 hrs[1] PM: 27 hrs	L: Biliary-major S: Renal-major	Can be taken without regard to food
o/p/r with d (Viekira® pak)	4-5 hrs D: 8 hrs	21-25/5.5/4/ 5.5-6hrs	Urine: 2-11.3% Feces: 86-94%	Relative to fasting conditions, o/p/r & dasabuvir with a moderate fat meal increased the mean AUC by 82%, 211%, 49%, and 30%, respectively
sofosbuvir/velpatasvir /voxilaprevir (Vosevi®)	S: 2 hrs VEL: 4 hrs VOX: 4 hrs	S: 0.5 hrs VEL: 17 hrs VOX: 33 hrs	S: 80% R/14% F VEL: 0.4%/94% VOX: 0%/94%	Take with food
velpatasvir/sofosbuvir (Epclusa®)	S: 0.5-1 hr V: 3 hrs	S: 0.5 hr V: 15 hrs	S: 80% R/14% F V: 0.4%R/94% F	Can be taken without regard to food

[a] elimination half-life [1]Metabolite: 27 hrs PM: primary metabolite of sofosbuvir

o/p/r-d: ombitasvir/paritaprevir/ritonavir w/dasabuvir (Viekira® pak)

CLINICAL TRIALS

When treating hepatitis C virus (HCV) infection, the goal of therapy is to eradicate the infection, as well as to prevent complications. Prior to 2013, there was insufficient data to suggest that monotherapy with ribavirin would accomplish these therapy goals. Instead, data suggested that the preferred treatment regimen is a combination of peginterferon alfa and ribavirin. Two different formulations of peginterferon alfa are

currently available: peginterferon alfa-2a and peginterferon alfa-2b. Peginterferon alfa-2a has a standard weekly dose of 180µg, whereas peginterferon alfa-2b is weight based at 1.5µg/kg once weekly. [1] With the FDA approval of sofosbuvir (Sovaldi®) and other additional medications, there are now treatment regimens available for HCV without the need for peginterferon-alfa or interferon alfacon.

During the process in which peginterferon alfa-2b gained FDA approval, it was combined with ribavirin at either one flat dose or at a weight-based dose. The results from these clinical trials led to approval for use of peginterferon alfa-2b to be combined with one flat-dose ribavirin. However, further analysis of this data suggested a strong linear dose/response relationship between ribavirin and sustained virologic response (SVR). This suggested that a superior SVR would be observed if peginterferon alfa-2b was combined with a higher, weight-based dose of ribavirin. It is now indicated to use peginterferon alfa 2-b with weight-based ribavirin dosing.

A 2007 study by Jacobson et al[3] examined a comparison of weight-based ribavirin compared to a flat-dose of ribavirin when added to peginterferon alfa-2b therapy. The trial has become known as the WIN-R Study. This was a prospective, multicenter, community-based and academic-based, open label, investigator-initiated study conducted in the United States. A total of 5,027 patients were included in the study and assigned randomly to receive peginterferon alfa-2b plus a flat-dose of ribavirin or peginterferon alfa-2b plus a weight-based dose of ribavirin. SVR was higher in the weight-based ribavirin group compared to the flat-dose ribavirin group (44.2% vs. 40.5% respectively); the investigators, however, did not indicate whether this difference was significant and such results are probably not clinically meaningful.

Large, randomized, controlled trials have shown that SVR is higher with combination therapy compared to peginterferon or ribavirin used as monotherapy (neither of which are indicated for monotherapy use). In 2005, the first study was published that examined this hypothesis. This study was a decision analysis model comparing peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin. The model also included a group of patients treated with peginterferon alfa-2b plus a weight-based dose of ribavirin. In addition to looking at the SVR, the early virologic response (EVR) was assessed at 12 weeks of therapy for patients with genotype 1 HCV. EVR is defined as a 2-log decrease in viral load following 12 weeks of therapy. It is thought that nonresponders to therapy, based on EVR, should discontinue therapy following the initial 12 weeks of treatment. The SVR for the two flat-dosed ribavirin therapies were nearly identical (53.6% and 53.8%). However, the group with combined peginterferon alfa-2b plus a weight-based dose of ribavirin had an SVR of 61.4%.[8]

Meta-Analysis/Reviews: Peg A vs Peg B

Awad et al[25] performed a 2010 systematic review of 12 randomized clinical trials (N=5,008) comparing peginterferon alfa-2a plus ribavirin vs. peginterferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C. Overall, peginterferon alfa-2a significantly increased the number of patients who achieved an SVR vs. peginterferon alfa-2b (47% vs. 41%). Subgroup analyses of risk of bias, viral genotype, and treatment history yielded similar results. A meta-analysis of adverse events leading to treatment discontinuation included 11 of the 12 trials and revealed no significant differences between the two peg-interferons. The investigators did note, however, a significant lack of evidence on adverse events which curbed their decision to definitively recommend one peginterferon over the other, since any potential benefit must outweigh the risk of harm.

A similar meta-analysis was published by Zhao et al[59] in 2010 comparing peginterferon 2a to peginterferon 2b therapy both in combination with ribavirin. A total of 7 clinical trials comprising of 3,212 patients were included and the results of this study were in agreement with the meta-analysis published by Awad et al. There was a significantly higher SVR in the peginterferon 2a (50%) compared to peginterferon 2b (46%; RR of 1.1, 95%CI: 1.02-1.2, p<0.05). This significant difference was not present in the subgroups of genotype 1 and 4 but was significant in genotypes 2 and 3. There was no difference between treatments in discontinuations due to adverse events; however, these events were few and the authors felt they could not recommend either regimen over the other at this time.

In 2011 Singal et al[75] conducted a meta-analysis of peginterferon alfa-2a vs. peginterferon alfa-2b in treatment naïve patients. A total of 9 trials were included in this analysis evaluating sustained virologic response (SVR) and treatment discontinuation. The results of the analysis are in agreement with the previously published studies by Zhao and Awad. There was a higher SVR in the peginterferon alfa-2a group compared to the alfa-2b group (OR 1.36, 95%CI: 1.07-1.73, p=0.011). There was no significant difference in treatment related adverse events between the groups (OR: 0.66, 95%CI: 0.37-1.16, p=0.15).

Yang et al[117] performed a 2013 meta-analysis of randomized trials evaluating the efficacy and tolerability of peginterferon alpha-2a and peginterferon alpha-2b plus ribavirin for chronic hepatitis C. Seven trials were selected from the literature including 1,845 and 1,823 patients who were randomly treated with peginterferonα-2a and peginterferon α-2b, respectively, both plus ribavirin. The overall sustained virologic response rate of the peginterferon α-2a group was significantly higher than that of the peginterferon α-2b group (46.7% versus 42.4%, p=0.01). The early virologic response and end-of-treatment response rates were significantly higher in the peginterferon α-2a group than in the peginterferon α-2b group (56.1% versus 49.8%, p < 0.0001; 67.9% versus 56.6%, p<0.00001, respectively). Current evidence suggests that peginterferon alpha-2a has superior efficacy than peginterferon alpha-2b for chronic hepatitis C patients.

Hauser et al[156] published a Cochrane review comparing the benefits and harms of peginterferon alpha-2a and peginterferon alpha-2b. 17 randomized clinical trials were included with a total of 5,847 patients randomized to take peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin. The two therapies had no significant differences in the rates of reported adverse events. Peginterferon alpha-2a significantly increased the number of patients who achieved SVR compared to peginterferon alpha 2b (51% versus 43% respectively; RR 1.12). The authors conclude that there is lack of evidence on patient-important outcomes and paucity of evidence on adverse events. Moderate quality evidence suggests that peginterferon alpha-2a is associated with a higher SVR in serum than with peginterferon alpha-2b, yet there is a high risk of bias within the included studies.

Meta-Analysis/Reviews: Non-Responders/Relapsers

A particularly important population was evaluated by Singal et al[64] in another meta-analysis evaluating re-treatment of patients who were nonresponders or relapsers to combination interferon and ribavirin therapy. A total of 18 trials were included for meta-analysis to determine the primary outcome of efficacy of re-treatment regimens. Nonresponders to peginterferon and ribavirin therapy had significantly increased SVR when therapy was extended to 72 weeks of PEG-INF 2a/ribavirin therapy whereas higher doses of PEG-INF 2a (360mcg/wk) had no effect on SVR rates. Similarly, higher doses of standard interferon (15mcg/d) did not improve SVR. Nonresponders to standard interferon and ribavirin therapy were more likely to have SVR

when treated with high doses of PEG-INF/ribavirin compared to conventional doses. Relapsers to combination therapy were more likely to attain SVR in high dose PEG-INF/ribavirin or in prolonged therapy (72wks) of standard interferon therapy. Lastly, the addition of amantadine therapy to relapsers of standard interferon and ribavirin therapy did not improve SVR rates compared to placebo. The significance of the results of this study is limited with the addition of the protease inhibitors to our treatment arsenal; however, it does provide guidance to those who may not tolerate the newer regimens.

Meta-Analysis/Reviews: Miscellaneous

Brok et al[23] conducted a 2009 review of ribavirin as monotherapy in 14 trials including 657 patients with chronic HCV. Outcome measures analyzed included SVR, liver-related morbidity plus all-cause mortality, and adverse events. Also assessed were end of treatment virological response, biochemical response (transaminase activity), and histological response. Compared with placebo or no intervention, ribavirin had no significant effect on SVR, liver-related morbidity plus mortality, or end of treatment virological response. Also noted was a significantly improved end of treatment biochemical and histological response but not sustained biochemical response, and a significant inferiority to interferon regarding virological and biochemical responses. In addition, ribavirin significantly increased the risk of adverse reactions, including anemia. Overall, the investigators found ribavirin monotherapy significantly inferior to interferon monotherapy or standard combination therapy and recommended its use only in randomized comparative trials.

A 2010 review by Brok et al[24] evaluated 83 randomized HCV trials involving 12,707 patients. Trials compared efficacy and safety of ribavirin plus interferon vs. interferon monotherapy. Primary outcome measures evaluated were SVR, liver-related morbidity plus all-cause mortality, and adverse events. Also, subgroup analyses of patients who were naive, relapsers or non-responders to previous antiviral treatment were performed. Compared with interferon, ribavirin plus interferon had a significant beneficial effect on SVR in subgroups of naive patients, relapsers, non-responders and in all patients. Morbidity plus mortality was significantly reduced in all patients but not in naive, relapsers or non-responders individually. Combination therapy significantly increased the risk of hematological, dermatological, GI, infectious, and miscellaneous (cough, dyspnea, fatigue) adverse reactions; likewise, combination therapy significantly increased the risk of treatment discontinuation and dose reductions. The authors concluded that compared with interferon alone, ribavirin plus interferon was more effective in clearing hepatitis C virus from the blood but that more evidence was needed regarding reduction in liver-related morbidity and all-cause mortality.

A meta-analysis published by Alavian et al[61] evaluated various dosing regimens for interferon (Infergen®) therapy in patients with chronic hepatitis C. The primary endpoint was SVR (undetectable HCV RNA levels 6 months after completion of therapy), where safety endpoints were withdrawals and dropouts, and dose modifications due to ADE's. A total of 10 studies were included (N= 1,600) with 75% of the patients representing treatment naïve status, and only 4 utilized combination ribavirin therapy. Comparison of high dose vs. low dose interferon therapy showed no improvement in SVR between the groups. The relative risk of withdrawal was not statistically significant; however, the RR for dose modification was higher in the high dose (18mcg or 15mcg TIW vs 9mcg TIW) groups (RR 3.82, 95%CI: 1.33-11). Patients treated with 9mcg TIW had a significant increased probability in achieving SVR compared to 3mcg TIW (RR 3.14, CI: 1.68-5.87, $p<0.001$). The reporting of adverse events was inadequate to conduct a meta-analysis. The authors conclude

that flat dosing of interferon is superior to induction therapy with higher doses but admit that the insufficient reporting of methodologies and adverse effects limits their conclusions.

A long-term follow-up study published by Swain et al[41] evaluated the SVR in patients treated with pegylated interferon therapies. Swain evaluated 1,546 total patients from 9 clinical trials and found 98.7% of patients continued to have SVR at a mean of 4 years after end of treatment in original studies. In patients treated with PEG-INF 2a (n=1,355), durable SVR did not differ between those treated with PEG-INF2a alone (98.8%) or in combination with ribavirin (99.2%). They conclude that SVR remains durable when patients are treated with PEG-INF 2a regardless of the treatment regimen.

The HALT-C trial published by Di Bisceglie in 2008 evaluated low-dose pegylated interferon therapy for 3.5yrs in patients who failed to achieve SVR with previous INF therapy. This study showed no reduction in preventing liver disease or death and was associated with increased mortality. A follow up study by Di Bisceglie et al[42] in 2010 evaluated mortality and possible causes for an additional 3 years in 1,050 patients. Mortality was higher in patients receiving long term low dose PEG-INF therapy (20% vs. 15%, p=0.049), with separation occurring at the end of the trial and continuing during the 3yr extended follow up. There were no significant differences between treatment and control with the combined death and liver transplantation outcome.

A study by Lok et al[45] in 2011 evaluated the long-term risk of developing hepatocellular carcinoma (HCC) or decompensated liver disease after follow-up for an additional 8.7 yrs after the end of the HALT-C trial. Overall, there was no statistically significant difference in HCC between treated patients (7.2%) and controls (9.6%; HR: 0.77, 95%CI: 0.51 to 1.18, p=0.24). When patients with cirrhosis at baseline were analyzed separately, there were significantly fewer treated patients with a diagnosis of HCC (HR 0.45, 95% CI: 0.24-0.83, p=0.01); this remained significant after adjusting for competing risks. Given the side effect profile of interferon therapy and the lack of overall mortality benefit in HALT-C, it is unlikely that PEG-INF therapy is a useful therapy for prevention of HCC.

Similarly, a population-based cohort study by Di Martino et al[73] utilized propensity adjusted analysis to determine the impact of antiviral therapy, with or without SVR, on the outcomes of cirrhosis decompensation, HCC, liver-related and non-liver related mortality. A total of 1,159 patients with HCV who received at least one course of interferon alfa monotherapy, interferon+RBV, or Peginterferon+RBV therapy were included. Overall, there was an SVR rate of 35.3% with a median follow up duration of 59 months. The rate of decompensated cirrhosis, HCC, and liver related death and non-liver related death at 5 years was 4.4%, 2.7%, 5% and 8.9% respectively. Alcohol consumption and an incidental HCV diagnosis were both independent risk factors for liver-related death. In a propensity matched subset, there was no significant benefit to antiviral therapy, however those who achieved SVR did not have instances of death.

Zhao et al[60] published a meta-analysis evaluating peginterferon therapies and interferon therapies in combination with ribavirin in the Chinese population. A total of 18 trials evaluating either regimen in patients of Chinese origin were included for a total of 1,148 patients. Overall, SVR was significantly higher in those patients treated with pegylated interferon therapy (64%) compared to interferon therapy (40%; RR 1.56, 95%CI: 1.28-1.91, p<0.01). This significance was primarily due to differences in response between pegylated interferon alfa 2a/ribavirin vs. interferon 2a/ribavirin. There were no differences between pegylated interferon 2b/ribavirin and interferon 2b/ribavirin. The subgroup of genotype 1 patients showed

similar benefit in SVR rates when treated with pegylated interferon compared to interferon. Differences between pegylated interferon alfa 2a versus 2b were not statistically significant nor were dropout rates between any of the therapies.

A 2010 study by Feuerstadt et al[32] regarding the effectiveness of pegylated interferon and ribavirin in an urban population of minority patients raised the questions of whether current treatments were actually as effective as many previous studies had suggested. These authors postulated that ethnic background influenced Hepatitis C kinetics and that the current treatments were not always available, appropriate or effective for all patient populations**.** They suggested that further investigation into these discrepancies were warranted.

A meta-analysis published in 2014 by Druyts et al[143] compares the efficacy measured by SVR of boceprevir (BOC), telaprevir (TEL), faldaprevir (FAL), simeprevir (SIM), and sofosbuvir (SOF) in combination with peginterferon-ribavirin (PR) against a control of PR. Adults with genotype 1 who were naïve to therapy were eligible for inclusion and 9 studies met the inclusion criteria. There were no statistically significant differences in each of the studies when comparing the regimens with and without PR. The pooled SVR of the included direct-acting antiviral regimens ranged from 63% (95% CI: 58–68%) for response-guided therapy BOC to 88% (95% CI: 78–97%) for response-guided therapy with SOF. These studies demonstrated that standard duration of therapy and response-guided therapy regimens of direct-acting antivirals plus PR do not differ greatly in terms of SVR among treatment-naïve hepatitis C genotype 1 patients.

Suwanthawornkul et al[175] conducted a systematic review and network meta-analysis in 2015 on the efficacy of second generation direct-acting antiviral (DAA) agents for treatment naive hepatitis C genotype 1. RCTs were reviewed and included only those with the second generation DAAs, such as simeprevir (SMV), sofosbuvir (SOF), declatasvir (DCV), ledipasvir (LDV), and paritaprevir/ritonavir/ombitasvir plus dasabuvir (PrOD). Primary outcomes assessed were SVR12 and SVR24 at the end of treatments. Among all DAAs plus PR (peg-interferon with ribavirin) regimens (i.e. SMV plus PR, DCV plus PR, and SOF plus PR), the comparison of SMV plus PR versus PR alone had sufficient data for performing direct meta-analysis of SVR12 (4 studies, n = 1,354) and SVR24 (5 studies, n = 1,252). Pooled RRs were 1.46 (95% CI: 1.28, 1.67) for SVR12 and 1.46 (95% CI: 1.26, 1.69) for SVR24, suggesting that patients receiving the SMV plus PR regimen were 46% more likely to have SVR12 and SVR24 than patients receiving PR alone.

The pooled incidence of SVR12 for PR, SMV plus PR, SOF plus PR, and DCV plus PR regimens were respectively, 51% (95%CI: 43%, 59%), 83% (95%CI: 79%, 86%), 82% (95%CI: 63%, 100%), and 65% (95%CI: 57%, 73%). A two-stage multivariate meta-analysis was applied and suggested that the chance of having SVR12 was significantly higher in SMV plus PR and DCV plus PR regimens when compared with PR alone. The pooled RRs for SMV plus PR and DCV plus PR were of 1.48 (95%CI: 1.27, 1.72) and 1.82 (95%CI: 1.24, 2.69). SOF plus PR regimen also increased SVR12 when compared to PR, but this did not reach statistical significance (pooled RR = 1.52; 95%CI: 0.97, 2.40). Treatment ranking was then assessed by estimating probability of being the best treatment, which yielded probabilities of 65.5%, 28%, and 6.5% for DCV plus PR, SOF plus PR, and SMV plus PR regimens, respectively. This indicated that the best treatment regimen was DCV plus PR followed by SOF plus PR. Pooled incidence of SVR24 for PR, SMV plus PR, SOF plus PR, and DCV plus PR regimens were 48% (95%CI: 40%, 57%), 83% (95%CI: 80%, 86%), 81% (95%CI: 68%, 95%), and 62% (95%CI: 53%, 70%). When compared with PR alone, all DAAs plus PR regimens significantly increased SVR24 with pooled RRs of 1.46 (95%CI: 1.22, 1.75), 1.98 (95%CI 1.24, 3.14), and 1.68 (95%CI: 1.14, 2.46) for

SMV plus PR, SOF plus PR, and DCV plus PR regimens. SOF plus PR regimen had the highest probability for being the best treatment (74.5%), followed by DCV plus PR (24.5%), and SMV plus PR (1%) regimen.

Swallow et al[168] conducted a comprehensive literature review published in 2016, comparing daclatasvir (DCV) + sofosbuvir (SOF), sofosbuvir + ribavirin (R), and peginterferon-alfa plus ribavirin in patients with hepatitis C genotype 3. The primary outcome of interest included SVR12. At 12 weeks post-treatment, the SVR rates were similar between patients treated with DCV + SOF and SOF + R in both the unadjusted and adjusted comparisons (before adjustment: 89.6 vs 85.2%; p = 0.216; after adjustment: 88.8 vs 85.2%; p = 0.537). Results were similar for the subgroups of treatment naive patients (before adjustment: 90.1 vs 94.3%; p = 0.262; after adjustment: 96.4 vs 94.3%; p = 0.458) and treatment-experienced patients (before adjustment: 88.4 vs 78.6%; p = 0.154; after adjustment: 83.2 vs 78.6%; p = 0.624).

The SVR rate was significantly higher among patients treated with DCV + SOF in both the adjusted and unadjusted comparison (before adjustment: 87.8 vs 66.5%, p < 0.001; after adjustment: 95.6 vs 66.5%, p < 0.001). In this adjusted indirect comparison, treatment with 12 weeks of DCV + SOF was associated with comparable efficacy and better tolerability than 24 weeks of SOF + R and greater efficacy and a lower rate of discontinuation than 24 weeks of peg-interferon alfa plus ribavirin. With its high efficacy and improved tolerability, in combination with shorter treatment duration, DCV + SOF is an important treatment option for HCV genotype 3 patients.

In 2015, Cui et al[177] conducted a meta-analysis that included seven RCTs (N=2,301) to assess for the safety and efficacy of simeprevir for the treatment of HCV genotype 1 infection. Studies assessed included only the use of simeprevir added to peginterferon and ribavirin (triple therapy) as compared to peginterferon and ribavirin alone (dual therapy). Results suggested that the triple regimen had a higher pooled SVR rate [odds ratio (OR) = 4.57; 95% confidence interval (CI): 3.34-6.27; p < 0.001)] and lower pooled relapse rate [relative risk (RR) = 0.41; 95% CI: 0.33-0.50; p < 0.001] than the dual regimen. The pooled incidence of adverse events (AEs) was comparable between the two regimens (RR = 1.01; 95% CI: 0.99-1.03; p = 0.339), whereas the incidence of serious AEs in the triple regimen was lower (RR = 0.7; 95% CI: 0.50-0.98; p < 0.05). The meta-analysis suggested that the addition of simeprevir to pegIFN and RBV is effective and well-tolerated in treating chronic HCV genotype 1 infection, with a low incidence of AEs.

In 2016, Andersohn et al[174] published a meta-analysis and historical comparison (also called non-adjusted indirect comparison) which compared study C212 (simeprevir + PegIFNα-2a + RBV in patients with chronic HCV-1/HIV coinfection) with studies and/or study groups in which HCV-1/HIV coinfected patients were treated with PegIFNα-2a + RBV only. This historical comparison (total of 12 relevant study groups.) provides first systematic evidence for the superiority of simeprevir + PegIFNα-2a + RBV compared to PegIFNα-2a + RBV alone in patients with HCV-1 and HIV coinfection. The absolute difference of the proportion of patients with SVR24 was approximately 45%, which is compatible with data from simeprevir RCTs that included non-HIV patients with HCV-1 infection. No increases in the frequency of important AE categories were identified; however, these analyses were limited methodologically and by the low number of studies contributing data to these comparisons. Additional data (for instance from observational studies) on the safety of simeprevir triple therapy compared to PegIFNα-2a + RBV alone and compared to other HCV treatment options would be desirable. The historical comparison revealed a substantially higher proportion of patients with SVR with simeprevir + PegIFNα-2a + RBV compared to PegIFNα-2a + RBV alone in patients with HCV-1 and HIV coinfection.

In 2016, Ampuero et al[198] published a meta-analysis that looked at the therapeutic efficacy of various treatment regimens in genotype 3. The article analyzed comparisons of PEG-INF based therapy including sofosbuvir (SOF) + RBV for twelve-week durations and with SOF + RBV for twenty-four weeks. Also included was an assessment of the importance of extending the course of SOF + RBV therapy from 12 or 16 weeks versus 24 weeks. Finally, the authors looked at the role of adding RBV to combination therapies SOF + daclatasvir (DCV) and SOF + ledipasvir (LDV). A total of twelve studies met criteria and were included. The authors concluded triple therapy including SOF + RBV + PEG-IFN could achieve higher SVR rates (92.5%; 236/255) than SOF + RBV (75.2%; 415/552), [OR = 3.51 (95%CI: 2.08-5.92)]. Studies also showed that a 24-week course of SOF + RBV was better than a 12- or 16-week course in terms of SVR rates [OR = 3.51 (95%CI: 1.59-7.70)]. When looking at adding RBV to SOF + DCV, the analysis found there was no advantage to achieve optimal SVR rates [OR =1.09 (95%CI: 0.35-3.40)]. The authors did find that adding RBV to SOF + LDV combination achieved better SVR rates [OR = 3.30 (95%CI: 1.35-8.04)] in certain circumstances.

In 2016, Ferreira et al[197] conducted a network meta-analysis that evaluated safety outcomes of Interferon-free (IFN) therapies for hepatitis C patients. A total of 51 randomized controlled trials were used for analysis with 13,089 subjects reviewed. The following IFN-free regimens were compared: ombitasvir in combination with paritaprevir, ritonavir and daclatasvir, sofosbuvir with velpatasvir, sofosbuvir alone, sofosbuvir with ledipasvir, asunaprevir with daclatasvir, and elbasvir used with grazoprevir (most treatment options were used with or without ribavirin). Differences were observed between ombitasvir in combination with paritaprevir, ritonavir, daclatasvir plus ribavirin and the following treatments: the same therapy but without ribavirin [OR 2.14 (95% CrI 1.09–4.44)], and elbasvir with grazoprevir [OR 4.09 (95% CrI 1.17–14.09)]. Other significant differences were observed when comparing sofosbuvir and ribavirin with sofosbuvir and velpatasvir [OR 2.07 (95% CrI 1.13–3.79)], and elbasvir with grazoprevir [OR 0.22 (95% CrI 0.07–0.72)]. The difference between elbasvir with grazoprevir and sofosbuvir with velpatasvir and ribavirin was significant [OR 0.19 (95% CrI 0.03–0.98)]. Placebo was significantly safer than two groups: ombitasvir in combination with paritaprevir, ritonavir, daclatasvir plus ribavirin [OR 2.40 (95% CrI 1.19–4.77)] and sofosbuvir with ribavirin [OR 2.69 (95% CrI 1.53–4.80)]. Elbasvir used with grazoprevir with or without ribavirin appeared to have a better safety profile than other IFN-therapies leading to less adverse events. The authors found no significant differences in serious adverse event outcomes.

Zhu et al[200] published a network meta-analysis of twenty-two randomized controlled trials that evaluated the efficacy of different direct-acting antiviral agent (DAA) interventions for improving SVR12 or SVR24 after the end of treatment. Their secondary outcome was the incidence of the most common adverse effects. All of the interventions, compared to peginterferon-ribavirin (PR), were simeprevir (SMV) plus PR, faldaprevir (FDV) plus PR, sofosbuvir (SOF) plus PR, beclabuvir (BEC) plus PR, daclatasvir (DCV) plus PR, and telaprevir (TLV) plus PR, and all showed significant clinical efficacy for SVR12. Therapies with boceprevir (BCV) plus PR, daclatasvir (DCV) plus PR, SMV plus PR, and SOF plus PR all provided significant benefits in improving SVR24 when compared with PR.

Authors ranked the likelihood of best treatment for all of the interventions evaluated and found DCV plus PR (57%) and SOF plus PR (28%) showed the highest improvement in SVR12 and SVR24 weeks. For adverse events, DCV plus PR was associated with the least fatigue and nausea but increased the incidence of insomnia and headache. BEC plus PR was associated with the least incidence of insomnia and headache.

In 2016, Loannou et al[211] performed a chart review for the Veterans Affairs (VA) nationally during an 18-month period from January 1, 2014 until June 30, 2015. A total of 17,487 patients were included in the analysis all of which were prescribed the direct antiviral agents (DAAs) sofosbuvir (SOF), ledipasvir/sofosbuvir (LDV/SOF), or paritaprevir/ritonavir/ombitasvir (PrOD). Patients were excluded if the regimens they were on were no longer used or recommended by the time the data was analyzed. The duration of therapy was determined as the total duration of the DAA prescriptions filled, and a course was considered terminated if the medications were not refilled within 45 days after the final prescription was exhausted. Early discontinuation of treatment occurred in 6.3% among all patients who inititated antiviral treatment and was more common in PrOD regimen. SVR rates overall were 90.7% and were higher in genotype 1 (92.8%) and genotype-4 (89.6%) infected patients. There was no significant difference in effectiveness between LDV/SOF and PrOD for genotype 1 patients. It was also found that the SVR difference between cirrhotic and non-cirrhotic patients were much smaller among genotype 1 than type 2 or 3, demonstrating the effectiveness of LDV/SOF and PrOD regimens in this population. In conclusion, the results demonstrated that LDV/SOF, PrOD, and SOF regimens can achieve high SVR rates in clinical practice, especially in genotype 1 patients. This study shows that even though these treatments are costly, they do appear to be effective in the real-world setting.

In 2016, a meta-analysis by Peng et al[118] assessed six RCTs including 1,100 adults with HCV with genotype 1-4 (genotype 1 accounting for 73.1%). The study was included if it was an RCT, consisting of patients aged 18-70 who had chronic HCV over 6 months. Patients in the experimental group were treated with daclatasvir with peg-IFN/RBV and the control group was treated with a placebo in combination with peg-IFN/RBV. In this meta-analysis, they wanted to assess the efficacy and safety of daclatasvir with pegIFN-α and ribavirin in chronic HCV. Rapid virologic response (RVR) was assessed, and it was found that the overall RVR rate was significantly higher in the daclatasvir group (46.43%) compared to the control (18.97%; $p<0.0001$). Additionally, it was found that the overall SVR24 rate was significantly higher in daclatasvir (65.08%) compared with the control (47.77%, $p<0.0001$). The treatment group showed a significant difference of RVR in both 60mg/day and 10mg/day groups compared to the control group; when examining the SVR24 between these two dose groups, statistical significance was reached only for the 60mg/day group and not the 10mg/day group. However, there were significant differences between the treatment and control group when comparing relapse rates and treatment discontinuation due to an adverse event. In summary, this meta-analysis indicated that high-dose daclatasvir (60mg/day) in combination with peg-IFN-α/RBV was effective and safe in treating chronic HCV GT1 infection.

In 2017, a meta-analysis by Borba et al[219] included 16 randomized controlled trials (N=7,171) to compare the efficacy among the first and second generation direct-acting antiviral agents with placebo and with standard dual therapy (peg-IFN + RBV) in terms of RVR and SVR24. The included RCTs assessed regimens with DAAs in treatment-naïve and treatment-experienced individuals who were chronically infected with HCV GT1. For the thirteen studies that reported RVR as a treatment outcome, statistically significant results were obtained for regimens with daclatasvir (DCV) 10mg, and for all evaluated dosages of grazoprevir, simeprevir (SIM), telaprevir (TVR) and boceprevir (BOC) versus therapies with placebo or standard dual therapy. The most efficacious treatment in terms of RVR was DCV 10mg + peg-IFN + RBV for 48 weeks with the least effacicous being placebo with peg-IFN and ribavirin for 48 weeks. Fifteen of the studies, which reported SVR24 as a treatment outcome, and statistically significant differences were found with SIM and BOC versus placebo. The most efficacious treatment regarding SVR24 was DCV 10mg + peg-IFN and RBV for 48 weeks. Daclatasvir

had the best result in terms of benefit-risk ratio for safety and telaprevir had the worst results. In summary, it was confirmed that DAAs were superior over placebo and dual therapy, as well as greater efficacy and benefit-risk of daclatasvir in comparison with other DAAs and standard dual therapy.

In 2017, Ferreira et al[220] performed a pairwise meta-analysis to compare the efficacy and safety of treatment with ledipasvir/sofosbuvir (LED/SOF) with or without ribavirin (RBV) in patients with HCV genotype 1. For the RCT to be included in the review, it had to have patients who were infected with HCV genotype 1 with or without cirrhosis but could not have any other comorbidities. The primary outcome of this study was to evaluate how many patients achieved SVR12 on LED/SOF with or without RBV, but also looked at rapid virologic response (RVR), viral relapse, and safety outcomes. After conducting their literature search, the investigators included seven studies which evaluated 2,567 patients; these studies were mostly conducted in the United States and all but one trial was multicenter. The patients most often were treated for 12 weeks, had genotype 1a, did not have cirrhosis, and were treatment naïve. The pairwise meta-analysis did not reveal any significant difference in efficacy between LED/SOF versus LED/SOF + RBV. In conclusion, it is recommended that in non-cirrhotic treatment-experienced or naïve patients with GT1, that treatment with LED/SOF for 12 weeks is recommended and is adequate to achieve treatment success. Both the EASL and AASLD guidelines suggest the combination of LED/SOF with RBV for 12 weeks in those who are treatment-experienced cirrhotic patients, however, if a patient is ineligible to use RBV, treatment should be 24 weeks with just LED/SOF. It is still unclear due to so many differing results whether it is necessary to combine the second generation DAAs with RBV for cirrhotic treatment-experienced patients.

In 2016, Alavian et al[222] completed a meta-analysis that included 55 studies to evaluate the efficacy of daclatasvir (DCV)-based regimens. Regimens that included DCV were: DCV/asunaprevir (ASV), DCV/ASV/beclubavir (BCV), DCV/peg-IFN/RBV with or without ASV, DCV/simeprevir (SIM), DCV/ sofosbuvir(SOF). In patients who had GT1b and were treatment experienced, DCV/ASV without ribavirin achieved SVR12 of 86.74%, and in treatment naïve patients, the SVR12 was 91.04%. In patients who were GT1b and treatment naïve, they achieved a SVR12 of 99% while on DCV/ASV/BCV, whereas GT1a patients had a SVR12 rate of 89.7%. Patients who were on peg-IFN/DCV regimen had GT4 and were treatment-experienced and achieved an SVR of 100%, compared to those who had GT1 had a SVR of 60.3%; however, it is important to note that there were only 12 patients with GT4 from that specific study. The next sub-set of patients were those who used DCV/SIM with or without RBV; these patients had GT1 and an SVR of 50% and 83.33%, with and without RBV, respectively. Lastly, patients who were treated with DCV/SOF were GT1 and their SVR rates were compared if they had liver disease or not. The patients who did not have severe liver disease had higher SVR rates than those with severe liver disease when treated for the standard 12 weeks; however, when patients with severe liver disease were treated for 24 weeks, they had just as high SVR rates as those without liver disease on 12 weeks of treatment. In conclusion, DCV is efficacious and safe and can be combined with a variety of other DAAs making it a good choice for HCV treatment. It is important to interpret these results carefully however because of the small sample sizes since studies were included as long as they had 10 or more participants.

In 2016, Li et al[224] conducted a meta-analysis that included 11 studies (N=264) to assess the efficacy and safety of direct-acting antivirals-based therapies for HCV patients with stage 4-5 chronic kidney disease. A majority of the studies used sofosbuvir-based regimens (SOF/SIM, SOF/DCV or RBV). The SVR12 rate for patients on sofosbuvir-based regimens was 89.4% while non-sofosbuvir regimens had a rate of 94.7%. The overall pooled SVR12 rate was 93.2%. In conclusion, the investigators were able to show safety and efficacy

with DAA-based regimens for HCV patients with stage 4-5 CKD with sofosbuvir regimens. However, it has been shown that there is efficacy with DAA regimens without sofosbuvir and ribavirin for patients with HCV and stage 4-5 CKD.

In 2017, Tao et al[225] conducted a meta-anaylsis that included 7 studies (N=26,260 to assess the efficacy and safety of ledipasvir and sofosbuvir (LDV/SOF) with and without RBV in treating HCV genotype 1 patients. Nineteen percent of patients enrolled had cirrhosis. Studies were excluded if the participants were co-infected or had advanced diseases. When comparing SVR12 rates, there was no statistical difference between LDV/SOF and LDV/SOF/RBV for patients with HCV GT1. There also was no difference between lengths of treatment duration or between treatment experienced or naïve patients. In conclusion, the meta-anaylsis shows that LDV/SOF based therapy was generally effective and safe in most patients with chronic HCV GT1 infection.

In 2017, Liao et al[226] completed a systematic review and meta-analysis to evaluate the efficacy and tolerability of sofosbuvir/daclatasvir (SOF/DCV) regimen with or without ribavirin in the post-liver transplant setting. The primary outcomes assessed were SVR12 and treatment-related side effects. A total of 7 studies were included in this review with 379 liver transplant recipients, who were treated for at least 12 weeks and primarily were GT1. The pooled rate of SVR12 was 93.3%. In 3 studies, there was a higher SVR12 rate in those treated with DCV/SOF versus those who were treated with DCV/SOF/RBV (OR 0.33, p=0.02). The most common side effects were anemia, infections, neutropenia, and renal failure. Some of these side effects could be contributed to RBV since the increase risk of hematological diseases has been documented. In summary, the data suggests that the regimen based on DCV/SOF with or without RBV presented a high SVR12 rate, and data from 3 studies indicated that DCV/SOF alone may provide a higher probability of cure.

In 2017, Yao et al[227] completed an efficacy and safety analysis to better determine the safety and efficacy of grazoprevir (GZR) plus elbasvir (EBR) in patients with HCV GT1 infection as well as provide the evidence for choosing the optimal treatment regimen. Patients with or without cirrhosis received a fixed dose of 12 or 18 weeks of GZR 100mg and EBR 50mg once daily with or without RBV. There were three clinical trials included in the analysis with a total of 777 patients enrolled. The overall SVR12 rate was 95% and SVR12 rates were 94% and 97% for those receiving 12 weeks of treatment versus 18 weeks of treatment, respectively. The most common adverse effects were fatigue, headache, nausea, and asthenia; more adverse events occurred when patients were taking GZR/EBR/RBV compared to just using GZR/EBR alone. There were no significant differences between all subgroups for the rate of SVR12. In summary, this analysis showed that the combination of GZR/EBR was effective and well-tolerated for the treatment of HCV GT1 infection, and that adding RBV may be of little benefit except in those who are treatment experienced.

In 2016, Ahmed et al[229] conducted a systematic review and meta-analysis focusing on the efficacy and safety of ledipasvir plus sofosbuvir (90/400mg) with and without ribavirin for the treatment of patients with HCV GT1. Eight clinical trials were included in the analysis with a n=1,892. The double regimen of LDV/SOF for 12 weeks treatment duration achieved SVR12 rate of 97.5% in non-cirrhotic patients and 89% in cirrhotic patients. Adding RBV to the regimen achieved SVR12 rates of 99.6% and 89% in non-cirrhotic and cirrhotic patients, respectively. The double regimen for treatment duration of 24 weeks achieved SVR12 rates of 99.6% and 92.6% in non-cirrhotic and cirrhotic patients. Adding RBV achieved SVR12 rates of 99.6% and 97.3% in non-cirrhotic and cirrhotic patients. The regimens with RBV were not superior to the double regimen without ribavirin in terms of SVR12, RVR, and SVR4. In summary, the double regimen achieved high

SVR rates in both non-cirrhotic and cirrhotic HCV GT1 patients after 12 and 24 weeks. The addition of RBV may improve the SVR for patient with HCV GT1 infection after 12 and 24 weeks. However, the difference was not significant with the current sample size.

In 2017, Wedemeyer et al[253] conducted a manufacturer-sponsored meta-analysis for patients with HCV genotype 1 or 4 infections, including those with compensated or decompensated cirrhosis, prior HCV treatment, and end-stage renal disease on dialysis. The meta-analysis was comprised of 5,158 patients that were treated with ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin (OBV/PTV/r±DSV±RBV). The majority (97.8%, n=5,046) of the studied patients had HCV genotype 1; the remaining 2.2% (n=112) had genotype 4. For special populations, 62.8% (n=3,240) had cirrhosis, 3.7% (n=189) had Child-Pugh B or decompensated cirrhosis, and 1.3% (n=67) had ESRD.

Subgroup analyses by patient subgroup were analyzed for SVR and safety. Patients with genotype 1a, 1b, or 4 had an SVR rate of 93.8% (95% CI, 87.8-98.0), 97.9% (95% CI, 97.0-98.9), and 98.9% (95% CI, 94.2-100), respectively. Treatment-experienced patients with genotype 1 had SVR rates greater than 95% for both groups. The presence of cirrhosis decreased the SVR rate slightly in genotypes 1a (93.9%) and 1b (98.0%), compared to those without cirrhosis in genotypes 1a (96.5%) and 1b (98.9%). The only available data for cirrhotic patients with genotype 4 came from 19 patients, for which they achieved an SVR rate of 99%, compared to 100% of those without cirrhosis. Patients with ESRD achieved an SVR rate of 97% when treated with OBV/PTV/r±DSV, compared to 92% of patients with Child-Pugh B or decompensated cirrhosis treated with OBV/PTV/r±DSB±RBV, in spite of its contraindication in this population.

For genotype 1, only 3.12% (n=2,370) experienced at least 1 serious side effect, 2.5% (n=5,170) of patients discontinued their medication, 1.28% (n=3,524) had virologic relapse, and 0.96% (n=3,440) experienced hepatic decompensation, for which 70% of this patient population had cirrhosis. Lastly, 0.53% (n=4,690) of patients died during treatment or follow-up. No patients with genotype 4 discontinued the medication, out of 42 patients where data was available. The subgroup of patients who had ESRD with or without dialysis did not require dose adjustments when treated with OBV/PTV/r±DSV, although 22% (n=67) of patients experienced anemia during the treatment course. Hepatic decompensation in patients with Child-Pugh B only occurred in 1 patient out of the 39 patients where data was reported. Overall, the real-world SVR rates for patients treated with OBV/PTV/r±DSV±RBV were high and safety was consistent with those demonstrated in phase III trials for those in all patient subgroups.

A recent 2017 Cochrane Review[250] of chronic hepatitis C included a total of 25,232 patients, assessing 51 different direct-acting antiviral agents, which was split between ‘on the market and under development’ or ‘withdrawn and discontinued’ medications. The 138 trials analyzed in this review were conducted from 2004-2016, averaging 14 weeks in duration. Patients in the included trials had HCV genotypes 1-6 and were either treatment-naïve and treatment-experienced. The primary outcomes of the meta-analysis were hepatitis-C related morbidity, serious adverse events, and quality of life. Secondary outcomes were all-cause mortality, ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy, hepatocellular carcinoma, non-serious adverse effects, and SVR.

Although very low quality, there was no evidence of a difference in all-cause or hepatitis-C-related morbidity in the meta-analysis for ‘on the market and under development’ DAAs (OR 3.72, 95% CI 0.53-26.18, p=0.19, 11 trials). There was also no difference in serious adverse effects (OR 0.93, 95% CI 0.75-1.15, p=0.52, 43

trials). When analyzed separately, the only DAA agent to show a significant difference for the risk of serious adverse effects was simeprevir (OR 0.62, 95% CI 0.45-0.86); however, the Trial Sequential Analysis did not confirm this result. Lastly, with Trial Sequential Analysis confirmation, the 'on the market and under development' DAAs appeared to reduce the risk of no SVR (RR 0.44, 95% CI 0.37-0.52, p<0.00001, 32 trials).

Similarly, for 'withdrawn and discontinued' DAAs, there was no evidence of a difference in all-cause or hepatitis-C-related morbidity in the meta-analysis (OR 0.64, 95% CI 0.23-1.79, p=0.40, 5 trials). Although, withdrawn DAAs were seen to increase the risk for serious adverse events (OR 1.45, 95% CI 1.22-1.73, p=0.001, 29 trials), but the Trial Sequential Analysis did confirm this result.

All-cause mortality, non-serious adverse effects, and SVR were the only secondary outcomes that were able to be analyzed in the included trials since there was not enough useful data to analyze the other secondary outcomes. Furthermore, the only effects that could be confirmed were short-term, limiting the results of this review. Overall, the trials and, subsequently, this review's results were at a high risk for bias, but despite the high external validity, the results of the meta-analysis likely overestimated the benefit and underestimated the actual harm of DAAs to patients for the treatment of HCV.

Treatment regimens with grazoprevir and elbasvir (G/E) (with or without ribavirin) in patients with HCV genotypes 1, 4, or 6 infections with compensated cirrhosis were assessed in an integrated analysis of 6 international trials conducted by Jacobson et al[278]. Patients were either treatment-naïve or experienced with peg-interferon, RBV with or without a first-generation protease inhibitor. Studies in this analysis included one with patients with stage 4 or 5 CKD and those with HIV co-infection. A total of 402 patients were included in this analysis and were treated for 12 weeks if they were treatment-naïve or 12, 16/18 weeks if treatment-experienced. In treatment-naïve patients with genotypes 1 and 4, SVR was achieved by 97.8% (135/138) without ribavirin and 90.3% (28/31) of those treated with ribavirin for 12 weeks. There were 3 virologic failures in each arm. SVR rates of treatment-experience patients were 91.4% (74/81), 88.9% (48/54), 100% (49/49), and 93.9% (46/49) for those treated with or without ribavirin for 12 weeks or 16-18 weeks, respectively. In evaluating predictors of response, patients with genotype 1a were found to most likely have virologic failure; those with and without baseline resistance-associated substitutions in nonstructural protein 5A with genotype 1a treated with G/E for 12 weeks, 73% (8/11) and 98% (96/98) achieved SVR, respectively. Drug-related side effects were more common in regimens containing ribavirin (73.1% vs 42%) and were fatigue, headache, nausea, and insomnia. No patients experienced hepatic decompensation during treatment or in follow-up. Overall SVR rates with G/E were high, ranging from 89%-100% in the studied patient population; however, the addition of ribavirin did not show benefit in those treated for 12 weeks. A ribavirin-containing regimen may be necessary for those with difficult to treat infections, such as genotype 1a and baseline resistance polymorphisms. However, G/E was generally well-tolerated and effective in treating those with compensated cirrhosis.

Ahmed et al[283] studied the safety and efficacy of ombitasvir/paritaprevir/ritonavir (PrO) and dasabuvir (PrOD) with and without ribavirin in patients with HCV genotype 1 infection. Outcomes assessed included SVR, virological, and relapse rates, in addition to safety. 94% of patients treated with PrO for 12 weeks achieved SVR, 0.03% had virologic failure, and 0.027% relapsed. Extending the treatment duration to 24 weeks, 98%, 0.3%, and 1.2% were the corresponding SVR, virologic failure, and relapse rates, respectively. When treating with PrOD for 12 weeks, patients achieved an SVR rate of 97%, and 1% had both virologic failure and relapse. The addition of ribavirin to the treatment regimen resulted in an SVR rate of 97% and

0.08% and 1.5% for virologic failure and relapse. Overall, there were no statistically significant differences with or without ribavirin (SVR: RR=1, p=0.84, virologic failure: RR=2.18, p=0.21, and relapse: RR=4.62, p=0.84). The adverse effects for the regimens studied were mild to moderate in intensity and occurred in 73% and 86% in regimens without and with ribavirin, respectively. Pooled risk ratios for nausea (RR=0.45), fatigue (RR=1.16), pruritus (RR=0.51), and insomnia (RR=0.32) favored PrOD+ribavirin over PrOD. However, headache (RR=0.95), diarrhea (RR=1.16), decreased hemoglobin <8g/L (RR=0.32), ALT >5x upper limit of normal (RR=0.37), and AST >5x upper limit of normal (RR=2.27) were comparable between the 2 groups. A regimen containing ombitasvir/paritaprevir/ritonavir was efficacious and generally well-tolerated in patients with genotype 1 infection, and an increased SVR rate was achieved with the addition of dasabuvir, however the addition of ribavirin to the treatment regimen did not significantly increase SVR rates nor decrease virologic failure rates.

In 2018, Ji et al[288] conducted a systematic review with meta-analysis to study the effectiveness and tolerability of interferon (IFN)-free direct-acting antiviral (DAA) treatment for HCV genotype 1(GT1) infected patients in Asia. Studies that enrolled adult patients with HCV GT1 infection in routine clinical practice in Asia, using IFN-free DAA regimens with sustained virologic response (SVR) reported at 12 or 24 weeks were included. The pooled SVR rates were computed with a random-effects model. Subgroup analysis and meta-regression were performed to determine how different variables may have affected the pooled estimates. 41 studies were included comprising of 8574 patients. The pooled SVR rates for GT1 were 89.9% with daclatasvir/asunaprevir (DCV/ASV) and 98.1% with ledipasvir/sofosbuvir ± ribavirin (LDV/SOF ± RBV). Baseline cirrhosis but not prior treatment history and age attenuated the effectiveness of both regimens. Baseline resistance associated substitutions (RASs) severely attenuated SVR of DCV/ASV and only minimally with LDV/SOF ± RBV (94.5% vs 99.2%, p=0.003). Patients with renal dysfunction treated with DCV/ASV showed a higher SVR rate (93.9% vs 89.8%, p=0.046). Patients with hepatocellular carcinoma (HCC) LDV/SOF ± RBV achieved a lower SVR than those without HCC (94.1% vs 98.7%, p=0.001).

He at al[332] published a meta-analysis of studies evaluating the effectiveness of direct-acting antivirals for patients with hepatitis C virus (HCV) and hepatocellular carcinoma (HCC). The primary study outcome was intention-to-treat (ITT) SVR, defined as an HCV RNA level less than the lower limit of quantitation (or undetectable) at 12 or 24 weeks after the end of HCV treatment. Fifty-six studies with 5522 patients with HCV and HCC were included. Fifty-three (95%) studies were observational cohorts (45 retrospective and eight prospective) and three studies were clinical trials. The pooled ITT SVR was 88.3% (95% CI 86.1-90.4), with a high heterogeneity across studies (p<0.001). In 27 studies enrolling both patients with prior or present HCC (n = 3126) and patients without HCC (n = 49 138), pooled SVR was 88.2% (95% CI 85.0-91.4, p<0.001) in the HCC population and 92.4% (95% CI 91.1-93.7, p<0.001) in the non-HCC population. Pooled OR of SVR among HCC population compared to no HCC population was 0.54 (95% CI 0.43-0.68, p<0.001), indicating significantly lower SVR among HCC population compared to non-HCC population. Fourteen studies reported SVR by DAA regimen. Pooled SVR was 76.3% (95% CI 60.4-92.1, p<0.001) in 208 patients who received suboptimal DAA therapy, 89.2% (95% CI 83.3-95.1, p<0.001) in 356 patients who received PI-containing DAA therapy and 96.9% (95% CI 94.3-99.4, p=0.01) in 856 patients who received sofosbuvir and NS5A inhibitor DAA therapy. In summary, the virologic response to DAA therapy was significantly lower in patients with prior or present HCC compared to those without HCC.

Ji et al[329] performed a meta-analysis of studies evaluating the effectiveness of direct-acting antivirals for patients with hepatitis C virus (HCV) and hepatocellular carcinoma (HCC). The primary outcome of this study

was the pooled SVR rate in patients with or without HCC, pooled SVR rate by regimen and/or genotype (GT). The final analysis included 49 full-text studies, comprising 3,341 patients with HCC and 35,701 without HCC. The overall SVR rate for all 39,042 patients included in the 49 studies was 91.8% (95% CI 90.5–93.0%). The overall SVR rate among patients with HCC (n = 3,341) was lower than in those without HCC (n = 35,701) (89.6%, 95% CI 86.8–92.1% vs. 93.3%, 95% CI 91.9–94.7%, p=0.0012). On meta-regression analysis, patients with HCC had a 4.8% (95% CI 0.2–7.4%) reduction in SVR rate compared to those without HCC. In stratified analyses by DAA regimen, SVRs in patients with HCC treated with any sofosbuvir (SOF)-based regimen (n = 1,694) were lower than SVRs of patients without HCC treated with SOF-based regimens (n = 26,355); 86.7%, 95% CI 82.1–90.8% vs. 94.6%, 95% CI 92.7–96.2%, p <0.0001). The same trend was noted for those treated with ledipasvir/sofosbuvir (LDV/SOF; 92.6%, 95% CI 85.9–97.5% [n = 884 HCC] vs. 97.8%, 95% CI 95.0–99.6% [n = 13,141 non-HCC], p=0.026) corresponding to a 9.2% (95% CI 3.0–13.2%) and 6.4% (95% CI 1.7 to 12.5%) reduction in SVR on meta-regression analyses, respectively. In contrast, SVR rates were similar in patients with or without HCC who received ombitasvir/paritaprevir/ritonavir ± dasabuvir (3D/2D) (97.2%, 95% CI 92.2–99.9% [n = 101 HCC], vs. 94.8%, 95% CI 92.3–96.9% [n = 5,438 non-HCC], p=0.79). In conclusion, SVR rates were lower in patients with HCC compared to those without HCC overall and especially in those with active HCC. Additional controlled studies are needed to study the impact of liver cancer on HCV cure rate in DAA-treated patients.

Lampertico et al[349] conducted a meta-analysis of observational studies to evaluate the "real-world" effectiveness and safety of glecaprevir/pibrentasvir for patients with chronic HCV infection. The primary outcome was the overall SVR12 rate in the ITT population (i.e., all patients treated with at least one dose of glecaprevir/ pibrentasvir who had SVR12 data available) stratified by genotype (GT) and the secondary outcomes included adverse event rates. A total of 18 cohorts involving 12,531 patients were included in the efficacy and safety analysis. SVR12 data from 8,583 patients were included in the meta-analysis of the ITT population (reported in 15 of the 18 studies). The results from the meta-analysis showed that overall SVR12 rates with glecaprevir/pibrentasvir were 96.7% (95% CI 95.4–98.1, I2 = 93.1%) in the ITT population. The SVR12 rate for GT1 (n = 1,972; 6 cohorts) was 95.7% (95% CI 92.6–98.8), for GT2 (n = 600; 8 cohorts) was 97.6% (95% CI 95.4–99.8), for GT3 (n = 1,162; 6 cohorts) was 95.0% (95% CI 92.0–98.0), and for GT4 (n = 121; 3 cohorts) was 99.0% (95% CI 97.2–100). No single AE was reported with a frequency above 5%; the most frequently reported AEs were pruritus (4.7%), fatigue (4.2%), and headache (2.7%). The results of this meta-analysis suggest that glecaprevir/pibrentasvir is an effective and well-tolerated pangenotypic treatment option for patients with chronic HCV infection in real-world clinical practice.

Wang et al[338] published a meta-analysis of studies evaluating the safety and efficacy of glecaprevir/ pibrentasvir (G/P) for chronic hepatitis C virus genotypes (GT) 1-6 infection. Data from eligible studies were pooled and sustained virologic response rates at 12 weeks post-treatment (SVR12) were calculated. Thirteen studies with 3082 patients were included and the total SVR12 rate of G/P with or without RBV in HCV patients including GT1-6 was 97.8% (95%CI, 96.7-98.7%). The majority of HCV-infected patients were treated with G/P 300 mg/120 mg and the pooled SVR12 was 97.9% (95%CI, 96.7–98.8%). A total of 177 patients from 2 studies received G/P 200 mg/120 mg therapy and the pooled SVR12 was 98.3% (95% CI, 95.2-99.9%). A total of 393 patients (13.5%) with G/P (300 mg/120 mg) treatment could not be analyzed according to GTs. The pooled SVR12 rates in GT1, GT2, GT3, GT4-6, and GT1,2,4,5,6 were 99.8% (95%CI, 99.1-100%), 99.2% (95%CI, 98.1-99.9%), 96.1% (95%CI, 94.2- 97.8%), 100% (95%CI, 99.3-100%), and 98.5% (95%CI, 97.3-99.5%), respectively. The SVR12 rate of 2977 patients treated with G/P without RBV was 97.9%

(95%CI, 96.8-98.8%). One hundred and five patients from 3 studies received G/P + RBV regimen and the pooled SVR12 was 98.2% (95%CI, 93.9- 100%). No drug related SAEs were observed. Eighteen patients discontinued treatment because of AEs. This meta-analysis suggests that the G/P regimen was highly efficacious in patients with HCV GTs 1-6 infection, including treatment-experienced and compensated cirrhotic patients. Adding RBV to a G/P regimen did not improve SVR12 rates. For patients without cirrhosis, 8 weeks of treatment may be recommended, whereas for DAA-naïve, compensated cirrhosis patients, 12 weeks of treatment may be recommended.

Meta-Analysis/Reviews: Sofosbuvir

Younossi et al[120] reported quality of life and work productivity questionnaire results of two trials[106,109] which included treatment with sofosbuvir (SOF). The first study included 201 patients with HCV genotypes 2/3 who were randomized to either 12 weeks or 16 weeks of sofosbuvir and ribavirin. The second trial was a single-group, open-label study of sofosbuvir, PEG-INF and ribavirin in 327 treatment-naïve adults with HCV genotypes 1, 4, 5 or 6. Among patients with HCV genotypes 2/3, fatigue, other patient-reported outcomes, and work productivity were reduced as compared with baseline; however, all scores returned to baseline levels or higher by week 4 of follow-up. By the end of 12 weeks of follow-up, most of the patient reported outcome scores showed significant improvement as compared with the baseline scores for the same subject groups. There were no differences in any of the metrics at any time point between the 12-week and 16-week duration periods of the study arms. This indicates that the addition of 4 extra weeks of SOF + ribavirin did not have additional negative or positive impact on patient reported outcomes. Among treatment-naïve genotypes 1, 4, 5 or 6 patients in the second study who were taking PEG-INF, ribavirin, and SOF, substantial decreases in most of the patient-reported outcomes scores were seen; however, the patient reported outcome scores either returned to baseline values or were significantly higher than the baseline scores after 12 weeks of follow-up. Nevertheless, those in study 2 (PEG-INF regimen) had substantially poorer patient reported outcomes and work productivity when compared with scores of those in the PEG-INF free regimen. Specifically, there were significantly smaller decrements in fatigue scores and work productivity scores in the PEG-INF free regimen vs the PEG-INF regimen. By week 4 of follow-up, the difference between the 2 regimens diminished, and by week 12 of follow-up, there were no further differences seen between the regimens. Further research is needed to validate these results.

Yang et al[135] conducted a meta-analysis of randomized controlled trials to evaluate the efficacy and safety of sofosbuvir for the treatment of HCV. Eight phase 3 studies were identified which evaluated a single identical primary endpoint of sustained virologic response (SVR) defined by HCV RNA less than the lower limit of quantification at 12 weeks after cessation of the therapy (SVR12). When the peginterferon in the peginterferon/ribavirin (PR) regimen was switched to sofosbuvir, the primary endpoint of sofosbuvir-containing regimen was superior to that of the regimen with peginterferon (74.3 vs. 66.7%, $p < 0.05$). Furthermore, when sofosbuvir was used as add-on therapy to the PR regimen, the absolute difference was larger (90.8 vs. 66.7%, $p<0.0001$). The new regimen consisting of sofosbuvir/ledipasvir showed an even greater improvement than the SR regimen (96.4 vs. 74.3%, $p< 0.0001$). There were no additional benefits with the inclusion of ribavirin (96.4 vs. 96.8%, $p < 0.05$). The overall odds ratio to achieve SVR12 in the eight clinical studies was 4.3 times greater in the sofosbuvir-containing arm (95% CI 3.54–5.10) than in the peg-interferon/ribavirin arm. The introduction of sofosbuvir to the HCV therapeutic arsenal opened the door to an all-oral regimen for the treatment of CHC infection, especially when causative virus is HCV GT 2 or 3.

Sofosbuvir is also offered an alternative treatment option for patients who are ineligible to receive peg-interferon because of severe adverse events or contraindications.

Yang et al[183] conducted a meta-analysis of the efficacy and safety of sofosbuvir for the treatment of hepatitis C virus infection. Eight studies with an identical primary endpoint (sustained virologic response at 12 weeks after cessation of therapy [SVR12]) were included in the analysis. When peginterferon was switched to sofosbuvir, the primary endpoint of sofosbuvir-containing regimen was superior to that of the regimen with peginterferon (74.3 vs 66.7%, p<0.05). Furthermore, when sofosbuvir was used as add-on therapy, the absolute difference was larger (90.8 vs 66.7%, p<0.0001). The new regimen consisting of sofosbuvir plus ledipasvir (SL) showed an even greater improvement than the sofosbuvir plus ribavirin (SR) regimen (96.4 vs 74.3%, p<0.0001). The overall odds ratio to achieve SVR12 in the eight studies was 4.3 times greater in the sofosbuvir-containing arm (95% CI 3.54-5.10) than in the ribavirin plus peginterferon (RP) arm. The adverse events (AE) reported during the eight clinical studies were 83.6 and 87.2% in the sofosbuvir and non-sofosbuvir arms, respectively. The most common AEs associated with the use of sofosbuvir were central nervous system disorder such as fatigue, headache, asthenia and insomnia. Sofosbuvir was safe and effective in the treatment of hepatitis C. Further studies are needed to evaluate the longterm persistence of the sustainced virologic response.

Swallow et al[182] performed a systematic literature review and subsequent matching-adjusted indirect comparison of daclatasvir and sofosbuvir versus sofosbuvir and ribavirin in patients with chronic hepatitis C coinfected with HIV. Of the 153 patients in ALLY-2 treated with 12 weeks of DCV+SOF, 62 were excluded (HCV genotypes 1 or 4, prior use of SOF, CD4 < 200, males with Hgb < 12 g/dl and other laboratory abnormalities) to match the enrollment criteria used in the PHOTON trials. In total, 91 of 153 patients from the ALLY-2 trial and 455 of 497 patients from the PHOTON trials were included in the analysis. At week 12 post treatment, the SVR rate was significantly higher among patients from ALLY-2 than among those from the PHOTON trials in both the unweighted and weighted comparisons (difference in SVR12 before weighting = 0.12; 95% CI, 0.07-0.17; P = 0.002; difference in SVR12 after weighting = 0.15; 95% CI, 0.12-0.19; P = 0.001). After adjustment, compared with patients treated with SOF+R, patients receiving DCV+SOF had a significantly lower rate of discontinuation due to AEs and significantly lower rates of the following specific AEs: cough, diarrhea, insomnia, nasopharyngitis, upper respiratory tract infection,and hemoglobin <10 g/dL. After adjustment for cross-trial differences in baseline characteristics, DCV+SOF was associated with a significantly higher SVR12 rate and lower rate of discontinuation due to AEs than SOF+R in patients coinfected with HIV and HCV. These results need to be validated with further research.

In 2015, Borba et al[189] published a systematic review and meta-analysis to assess the safety and efficacy of simeprevir and sofosbuvir for HCV genotype 3. There were 774 articles identified, of which 10 RCTs were selected for data extraction and statistical analysis. Simeprevir 100 mg promoted better SVR24 results than placebo, and simeprevir 150 mg was superior to placebo for the following outcomes: SVR12, SVR24, SVR12 rates according to METAVIR score for the subgroups F0-F2, F3 and F4; SVR12 rates according to HCV genotype for both genotype 1a and genotype 1b; SVR12 rates for HCV genotype 1a without baseline Q80K; and SVR12 according to IL28B genotype for CC, CT and TT. More viral relapse events were observed in the placebo group, for both evaluated doses. There were no significant differences for all of the evaluated safety outcomes between the simeprevir 100 mg and the placebo groups, and for almost all evaluated safety outcomes between the simeprevir 150 mg and placebo groups. Sofosbuvir promoted better SVR12 and

SVR24 than placebo. There was no difference in the safety of sofosbuvir and placebo groups for the majority of evaluated outcomes.

Nguyen et al[205] conducted a meta-analysis and systematic review that looked at the SVR rates in post-live transplant, HCV-1 infected, patients treated with simeprevir and sofosbuvir (SMV + SOF) ±ribavirin (RBV). Nine studies (325 patients) with ≥5 post-liver transplant HCV-1 patients treated with SMV + SOF ± RBV that had SVR12 data were analyzed. The pooled rate of SVR12 was 88% (95% CI 83.4% - 91.5%), which was lower than SVR12 rates in patients with non-liver transplants. There was a higher SVR12 rate in HCV-1a patients with mild fibrosis (93.6%) compared to those with advanced fibrosis (76.9%). Fatigue (21%), skin problems (15%), and headache (9%) were the most common side effects.

In 2016, a meta-analysis done by He et al[217] included 7 randomized controlled trials (N=2,601) with: patients who had GT1 HCV infection, that compared the efficacy and safety of triple therapy with dual therapy (triple=SOF/LDV/RBV and dual=SOF/LDV), and the main outcome measure was SVR12. Studies were excluded if the patients had a genotype other than 1, if the patients were co-infected, or if the study did not meet any of the other inclusion criteria. The primary outcome the investigators were interested in was SVR12, and they also looked at secondary outcomes which included: virological relapse, treatment discontinuation due to adverse events, and five main adverse events (nausea, headache, insomnia, fatigue, and anemia).

The SVR12 in genotype 1 HCV infection ranged from 70-100%, and when looking at the pooled data, there was no statistically significant difference in the overall proportion of patients achieving SVR12 between those who were on triple therapy compared to those on dual therapy. The triple regimen did not show a superior SVR in cirrhotic patients. Furthermore, relapse rates were comparable between those who used triple therapy and dual therapy (p=0.274). There was no difference between the two regimens related to treatment discontinuation due to side effects (p=0.274), but 2,026 out of 2,601 patients had at least one adverse reaction. In conclusion, the triple regimen for 12 or 24 weeks had similar efficacy as the dual regimen for the treatment of GT1 HCV infection. However, the 8-week triple therapy showed superior SVR12 when compared to the 8-week dual regimen, but the addition of RBV increased the risk of adverse events and the economic burden. Therefore, the 12 or 24-week dual regimen should be recommended as the first-line treatment for patients with HCV GT1 regardless of their prior treatment history and the presence or absence of cirrhosis.

A 2017 meta-analysis, conducted by Dolatimehr et al[251], was designed to determine the effect of a 12-week combination treatment of sofosbuvir (SOF) plus pegylated-interferon (pegIFN) and ribavirin (RBV) on patients with HCV genotype 1. A total of 5 articles were reviewed for the meta-analysis with a sample size of 411 patients. A treatment success rate of 88.5% was found for the combination of SOF + pegIFN + RBV for those with genotype 1. Prior to 2011, a regimen of pegIFN+RBV for 24-72 weeks was the standard of care, with only a success rate of 40-60%, numerous side effects, and a low threshold for resistance. With the newer, more expensive, but less widely available direct-acting antivirals (DAAs), they provide a lower risk of side effects, high resistance barrier, thus greater success rate; however, the more expensive medications are not always available in low-to-middle income countries. As a less expensive option of the new DAAs and with its addition to the regimen almost ensuring complete eradication of HCV from the body at week 4 and approximately 89% at weeks 12 and 24, this combination regimen of SOF/pegIFN/RBV is still a recommended option for those who cannot afford IFN-free regimens.

In a 2017 review by Stokes et al[252], the combination regimens of sofosbuvir (SOF) + ledipasvir (LDV) and SOF + LDV + ribavirin (RBV) were evaluated for noninferiority in treatment-experienced cirrhotic patients with HCV genotype 1. Unfortunately, genotype 1a and 1b could not be independently assessed due to the lack of patient-specific data. The primary outcome assessed was SVR12, but also the risk of adverse effects for both cirrhotic and non-cirrhotic patients. Two phase II and two-phase III trials were included in this analysis; of note, the pharmaceutical company, Gilead Sciences', played a substantial role in the development and funding of these studies. Overall, failure to achieve SVR12 rates ranged from 0-30% and 0-19% in treatment-experienced patients, for which they underwent 12 weeks of SOF/LDV and SOF/LDV/RBV, respectively. The pooled RR of those treated with 12 weeks of SOF/LDV compared to 12 weeks of SOF/LDV/RBV was 1.21 (95% CI: 0.42-3.42). Excluding Mizokami et al's study, the RR increased to 1.39 (95% CI: 0.39-4.97); the reason for this exclusion is that 96% of the patients in the study were genotype 1b compared to 13-21% of patients in the other studies. In terms of safety, the risk of having adverse effects, such as fatigue, rash, irritability, and anemia, was significantly greater in patients receiving the additional ribavirin (RR = 0.11, 95% CI: 0.04-0.29). Furthermore, there were 4 serious adverse effects, which occurred in the RBV group, although this was not significant. The results of this meta-analysis demonstrated that 12-week regimens of SOF + LDV cannot be considered noninferior to SOF + LDV + RBV in achieving SVR12 in cirrhotic, genotype 1, treatment-experienced patients, suggesting that until further research is conducted, 12 weeks of SOF + LDV + RBV is still the preferred, recommended treatment for this subgroup of HCV patients.

In a 2017 systematic review and meta-analysis by Ahmed[276] et al, 1,427 patients were included that had HCV infection genotypes 1-6 with and without cirrhosis. The regimens under investigation were 12 weeks of SOF plus velpatasvir (VEL) with and without ribavirin. SVR12 and relapse rates were the outcomes of interest, as well as safety. Except genotype 3 (RR 0.89, 95% CI 0.80-0.99, p=0.04), overall effect estimates did not show a favorable effect with the addition of ribavirin (genotype 1: RR=0.95, 95% CI 0.88-1.02, genotype 2: RR=1.00, 95% CI 0.66-1.51, genotype 4: RR=1.08, 95% CI 0.60-1.93). Again, effect estimates in terms of relapse rates did not favor the ribavirin regimen for genotypes 1 (RR 2.52, 95% CI 0.49-12.87, p=0.26) and 3 (RR 4.27, 95% CI 0.98-18.47, p=0.52). Safety was also assessed and pooled RRs for the most common adverse effects include nausea (RR=1.48, p=0.02), headache (RR=1.04, p=0.83), pruritus (RR=2.22, p=0.02), decreased hemoglobin level < 100g/L (RR=2.85, p=0.004), decreased hemoglobin level <85g/L (RR=5.13, p=0.07), serious adverse events (RR=0.83, p=0.54), and discontinuation due to AEs (RR=3.75, p=0.015). Subgroup analyses were also conducted looking into differences between genotype 1a vs 1b, cirrhosis vs no cirrhosis, and treatment-naïve vs treatment-experienced. Patients with genotypes 1a and 1b that were treated with SOF+VEL achieved SVR12 rates of 97.7% (p<0.001) and 99% (p<0.001), respectively. In terms of cirrhosis, 97.5% and 98.5% of genotype 1, 100% and 99.5% of genotype 2, 90.7% and 97% of genotype 3, 100% and 99.4% of genotype 4 achieved SVR12 in cirrhotic compared to non-cirrhotic patients, respectively (all, p<0.001). Lastly, both treatment-experienced and naïve patients with genotype 1 had 100% SVR rates, while 94.2% and 92.3% of genotype 3 patients achieved SVR, respectively. Overall, a single tablet regimen of SOF+VEL was associated with high efficacy and safety that was not affected by prior treatment exposure or compensated cirrhosis. There was no additional benefit of incorporating ribavirin into the regimen except for those with genotype 3.

Due et al[331] conducted a systematic review of the literature through December of 2018 and meta-analysis of studies evaluating direct-acting antivirals (DAA) for chronic hepatitis C genotypes 5 and 6. Thirteen studies involving 506 patients were included in the analysis. Four studies assessed the efficacy of four DAA regimens

in genotype 5 patients, which were mainly sofosbuvir (SOF) plus pegylated-interferon/ribavirin (PR) or other DAAs, with SVR12 ranging from 94.4% to 100%. Twelve studies assessed the efficacy of seven DAA regimens among genotype 6 patients, but only two DAA regimens (i.e., SOF + PR and SOF/ledipasvir) had sufficient data for pooling. The pooled SVR12 rates (95% CI) were 99.6% (92.2 to 100) for SOF + PR and 99.2% (96.5 to 100) for SOF/ledipasvir. These results suggest a high efficacy of DAA regimens (i.e., SOF + PR, SOF/LDV, and SOF/ VEL ± VOX) on genotype 5 patients, with the minimum SVR12 rate of 94.4%. Likewise, for genotype 6, all DAA regimens (i.e. SOF + RBV, SOF + PR, SOF/LDV ± RBV, and SOF/VEL ± VOX) showed high efficacy, where SVR12 rates ranged from 95% to 100%. Further larger scale randomized controlled trials in genotypes 5 and 6 are needed.

Pisaturo et al[348] published a meta-analysis of studies evaluating the efficacy of 12-weeks of velpatasvir and sofosbuvir-based regimen without ribavirin in patients with HCV with mild fibrosis who were naïve to previous DAA therapy. The primary outcome was sustained virologic response 12 (SVR12), undetectable HCV RNA 12 weeks after therapy completion. Sixteen studies were included in the analysis; a total of 6,453 subjects enrolled including 4,907 patients who met inclusion criteria for the definition of "patients without cirrhosis" and 1,371 patients who met the criteria for the definition of "patients without advanced fibrosis". Considering all the 4,907 subjects without cirrhosis included in the 16 studies enrolled, the prevalence of SVR by a 12-week sofosbuvir plus velpatasvir-regimen was 98% (95% CI: 96-99%). The prevalence of SVR was similar considering the 1,532 subjects from the 9 clinical studies and the 3,363 subjects from the 7 real-world studies (98%, CI 95%: 96-99% and 98%; CI 95%: 96-99%, respectively). Data indicate a prevalence of SVR of 99% (95% CI: 97- 100%) in the 3 studies enrolling 352 patients with HCV genotype 1, of 95% (95% CI: 94-96%) in the 2 studies enrolling 1,940 patients with HCV genotype 2, of 96% (95% CI: 93-99%) in the 6 studies enrolling 1,431 patients with HCV genotype 3 and 100% (95% CI: 98-100%) in the 3 studies enrolling 96 patients with HCV genotype 6. The results of this meta-analysis suggest that the single-tablet regimen of sofosbuvir plus velpatasvir is highly effective in chronic HCV patients without cirrhosis (SVR12 rate = 98%) and in HCV patients without advanced liver fibrosis (SVR12 rate = 96%). Furthermore, the prevalence of SVR was similar considering both clinical trials and real-world studies (98%, CI 95%: 96-99% and 98%; CI 95%: 96-99%, respectively).

Xue et al[336] conducted a meta-analysis of studies evaluating sofosbuvir-based (SOF) regimens with or without ribavirin (RBV) in patients with HCV recurrence after liver transplantation (LT). The primary outcome was sustained virologic response 12 weeks (SVR12) after the end of treatment. Twelve studies, comprising a total of 1466 LT recipients, were included in this study. The pooled SVR12 of these patients was 91% (95% CI: 84% to 95%). Nine articles provided available SVR12 rates for different genotypes, and the pooled SVR12 of genotype 1, 3 and other genotypes (genotype 2,4 and 5) were 92% (95% CI: 88% to 95%), 92% (95% CI: 74% to 98%) and 91% (95% CI: 77% to 97%), respectively. In total, 502 patients were treated with SOF-based DAAs + RBV (SVR12: 90%), and 964 patients were treated with SOF-based DAAs (SVR12: 94%). There was no statistical difference in SVR12 between the patients treated with SOF-based DAAs + RBV and those treated with SOF-based DAAs (RR = 0.97; 95% CI: 0.92 to 1.03; P = 0.35; I2 = 46%). Among these twelve studies, six showed an incidence of anemia with or without RBV. Anemia occurred in 103 of 243 patients (42%) who used SOF-based DAAs + RBV and in 66 of 694 patients (10%) treated with SOF-based DAAs. The pooled analysis showed a significant difference between the SOF-based DAAs + RBV group and the SOF-based DAAs group (RR = 5.18; 95% CI: 3.41 to 7.86; p < 0.00001). The results of this meta-analysis suggest that SOF-based antiviral therapy is effective in patients with recurrent HCV after LT, but the addition of RBV

does not contribute to a higher SVR rate. On the other hand, the addition of RBV significantly increased the incidence of anemia in patients.

Meta-Analysis/Reviews: Boceprevir and Telaprevir:

The protease inhibitor boceprevir (Victrelis®) has published articles evaluating their efficacy and safety in Hepatitis C genotype 1 patients. Each drug has a phase 2 study and 2 phase 3 studies evaluating its use in combination with peg-interferon alfa 2a or 2b in combination with ribavirin. Both medications have been studied in treatment naïve patients and patients who failed previous interferon and ribavirin therapy. At the time these drugs were introduced, they offered shorter treatment durations for those who responded early.

One meta-analysis of the direct acting agents boceprevir and telaprevir, when used in combination with pegylated interferon alpha and ribavirin, was conducted in 2012 by Cooper et al[76] evaluating the proportion of patients achieving SVR at the end of a 24-week post therapy follow up period, proportion of patients relapsing, and proportion of patients discontinuing treatment. A total of 10 phase 2 and 3 randomized, placebo-controlled studies with a total of 5,072 treatment naïve and treatment experienced patients were included. There was a significantly higher proportion of SVR in both treatment naïve and experienced patients treated with boceprevir (naïve: OR 1.91, 95%CI: 1.65-2.21; experienced: OR 3.09, 95%CI: 2.24-4.28). There was a significantly lower proportion of relapse in treatment-experienced patients treated with boceprevir (experienced: OR 0.36, 95%CI: 0.2-0.62). There was a significantly lower proportion of discontinuation in both treatment naïve and experienced patients treated with boceprevir (naïve: OR 0.65, 95%CI: 0.47-0.89; experienced: OR 0.54, 95%CI: 0.45-0.65). There was a significantly higher proportion of SVR (naïve: OR 1.69, 95%CI: 1.50-1.91; experienced: OR 3.86, 95%CI: 2.92-5.09), lower relapse rates in both treatment naïve and experienced patients treated with telaprevir (naïve: OR 0.30, 95%CI: 0.2-0.45; experienced: OR 0.21, 95%CI: 0.16-0.29). There was a lower proportion of discontinuation rates in treatment experienced patients treated with telaprevir (experienced: OR 0.61, 95%CI: 0.52-0.70).

When an indirect comparison was made between the two treatments when co-administered with peginterferon alpha plus ribavirin, results suggested that there were no differences between standard-dose duration of boceprevir and telaprevir regarding SVR, relapse to treatment, and discontinuation of treatment. An indirect comparison was done with regards to adverse events as well. Results suggested that naïve patients treated with a standard-dose of telaprevir regimen were more likely to develop a rash when compared with those treated with standard-dose of boceprevir regimen. Additionally, in naïve and experienced-treatment patients, a standard-dose telaprevir regimen was more likely to develop pruritus vs a standard-dose duration of boceprevir regimen. Significant differences with anemia and neutropenia were not seen between treatments. The authors concluded that significant differences in terms of major clinical endpoints were not seen between treatments. (**CHC Comments**: Please note that this is an indirect meta-analysis. This study was not set to determine non-inferiority.)

Wilby et al[77] summarized the data published on boceprevir and telaprevir in a 2012 review of the literature. He notes that typical SVR rates for standard of care peginterferon + ribavirin therapy is typically 40-50% in genotype 1 HCV patients. In phase 3 trials, boceprevir achieved a 67-68% response in a response-guided treatment naïve group and SVR rates of 59% and 66% in treatment-experienced patients in a response guided regimen and standard regimen group, respectively. In phase 3 trials, patients treated with telaprevir achieved response rates of 69% and 75% with better responses occurring in those treated for 12 weeks.

Additionally, in previously relapsed patient's treatment with telaprevir resulted in an 83%-88% SVR compared to only 24% in the control group. In nonresponders or partial responders SVR was 41%- 59%. Interestingly, the FDA has allowed the telaprevir monograph to be updated reflecting a response rate of 79% due to reclassification of those patients with negative viral loads at 12 weeks that did not have follow up values at 24 weeks. These patients were initially classified as treatment failures based on the original ITT principle.

In 2013, Manns et al[110] conducted a combined analysis of three randomized, controlled trials to evaluate the safety of boceprevir plus peginterferon alfa-2b and ribavirin in patients with chronic hepatitis C genotype 1. One study was open-label and two were double-blind. A total of 1,548 patients were treated with boceprevir-based triple therapy and 547 were treated with peginterferon and ribavirin dual-therapy. Over half of the patients in the dual-therapy arm (57%, 313/547) discontinued during the treatment phase, primarily because of treatment failure (37%, 202/547). In the triple-therapy arms, 37% (567/1,548) discontinued during the treatment phase, with 14% (215/1,548) of discontinuations attributed to treatment failure. Discontinuation because of adverse events was similar in the dual-therapy (12%, 67/547) and triple-therapy arms (13%, 205/1548). Only two adverse events, anemia and dysgeusia, occurred 20% more often with the triple-therapy regimen compared with the dual-therapy regimen. Nausea, diarrhea and neutropenia were the only other common events with an incidence of at least 5% greater when boceprevir was added to peginterferon and ribavirin. The proportion of patients with severe adverse events was 8% (43/547) and 11% (164/1548) in the dual-therapy and triple-therapy arms, respectively. While discontinuation rates due to adverse events were similar, hematologic and gastrointestinal side effects were more common when boceprevir was added to a dual-therapy regimen.

Park et al[111] performed a 2014 meta-analysis of telaprevir and boceprevir trials in patients with hepatitis C genotype 1. A total of 5,186 patients from 10 randomized controlled trials were included in the analysis. The probability of achieving SVR with triple therapy compared to dual therapy was statically significantly higher in 4 groups: (i) telaprevir-based triple therapy in treatment-naïve patients (RR = 1.62; 95% CI 1.47-1.78), (ii) telaprevir-based triple therapy in treatment-experienced patients (RR = 3.85; 95% CI 3.03-4.90), (iii) boceprevir-based triple therapy in treatment-naïve patients (RR = 1.70; 95% CI 1.56-1.86), (iv) boceprevir-based triple therapy in treatment-experienced patients (RR = 2.98; 95% CI 2.29-3.87). This meta-analysis suggested that triple therapies including either telaprevir or boceprevir are superior to dual therapy for both treatment-naïve patients and treatment-experienced patients in achieving better efficacy outcomes.

Special Populations:

Two specific meta-analysis evaluated treatment of chronic hepatitis C in the dialysis population. Alavian et al[62] evaluated factors associated with SVR in patients treated with pegylated or standard INF monotherapy. Twenty-one studies evaluating interferon and 12 evaluating pegylated interferon were included. The pooled SVR rates were 39.1% and 39.3% in standard and pegylated interferon therapies respectively. In standard interferon therapy, extension of therapy from 24 to 48 weeks resulted in a significant improved probability of achieving SVR.

A similar meta-analysis by Fabrizio et al[63] evaluated pegylated monotherapy in hemodialysis patients. The primary outcome of interest was SVR with secondary endpoints including measure of tolerability, end of

treatment virologic response (EOT-VR), end of treatment biological response (EBR) and sustained biochemical response (SBR). A total of 16 studies were included for analysis representing a total of 254 patients. The overall pooled SVR was 36% and dropout rate was 23%. The authors noted these response rates were similar to those achieved with standard interferon therapy. They conclude that pegylated interferon may not offer a benefit over standard interferon therapy in the dialysis patient population.

In 2008, the FDA approved the use of PEG-interferon alfa-2b + ribavirin for the treatment of HCV in children aged 3-17. In 2011, Wirth[74] published a review of the use of this regimen in pediatrics. A total of 5 prospective trials have been published with a total of 318 children receiving PEG-interferon alfa-2b or 2a therapy plus ribavirin. Overall, SVR was achieved in 60.7% of treated patients with 51% of genotype 1 patients achieving SVR, 93% of genotype 2 and 3, and 55% of genotype 4 achieving SVR. Overall relapse rates were 7.5% to 15% and 20% of patients experienced side effects. Wirth concludes PEG-interferon + RBV therapy should be considered standard of care, particularly for genotype 2 and 3 in children.

Zaini et al[65] published a meta-analysis evaluating the effectiveness and tolerability of peginterferon and ribavirin therapy in intravenous drug users (IDU). The primary outcome measure was SVR rate using intent to treat analysis; secondary outcome was dropout rates. The SVR for IDU's was 52% and was comparable to non-IDUs SVR rates of 50%. Outcomes were better in IDU patients with favorable genotypes (66% vs 44%, $p<0.001$) and in patients treated with peginterferon (48%) vs. recombinant interferon (40%; $p=0.049$). Dropout rates of 26% and psychiatric ADE rates were 2% and were comparable to non-IDU's rates. There was significant heterogeneity in the trials included in this meta-analysis; therefore, conclusions should be made with caution. Notably, 12 of the included studies incorporated collaboration between hepatologist and an addiction specialist into their protocol. A multi-disciplinary approach to hepatitis C therapy in IDUs is likely to be beneficial in achieving a good SVR.

Hou et al[116] conducted a meta-analysis of randomized trials evaluating the effect of antidepressants to prevent pegylated interferon-alpha/ribavirin-associated depression in patients with chronic hepatitis C. Six studies involving 522 patients met the inclusion criteria. The antidepressants used in these studies were escitalopram, citalopram and paroxetine. The rate of depression among 252 patients receiving an SSRI was 17.9% whereas the rate of depression among 261 patients receiving placebo was 31.0% (RR = 0.58, 95% CI 0.43-0.79). Four trials reported the effect of antidepressants on sustained virologic response (SVR). The rate of SVR among 176 patients receiving an SSRI and 184 patients receiving placebo was 56.8% and 50.0%, respectively (RR = 1.10, 95% CI 0.78-1.55). The rate of drug discontinuation was reported by all six studies. The SSRI group included 257 patients with a rate of discontinuation of 18.7%, while the placebo group included 265 patients with a rate of discontinuation of 21.1% (RR = 0.92, 95% CI 0.66-1.29). This meta-analysis revealed that prophylaxis with SSRIs can significantly reduce the incidence of PEG-IFN alpha/ribavirin-associated depression in patients with chronic hepatitis C.

In a 2018 meta-analysis by Ahmed et al[277], SVR and safety were assessed for those with HCV genotype 1 in a 12-week regimen of grazoprevir/elbasvir±RBV. A total of 8 studies were included with 1,297 patients. Outcomes assessed were SVR achievement and virologic relapse. Pooled SVR rate for grazoprevir/elbasvir was 94.3%, relapse rate was 2.1%, and virologic breakthrough rate was 0.4%%. The addition of RBV did not have increased SVR (RR=1, $p>0.05$), reduced virologic relapse (RR 1.20, $p>0.05$) and breakthrough rates (RR 1.36, $p>0.05$). There was also no significant difference in AEs for either regimen (serious AEs – RR 1.19, $p=0.65$; headache – RR 1.11, $p=0.76$; fatigue – RR 0.82, $p=0.58$; lowest Hb level on treatment – RR 0.67,

p=0.789; ALT/AST elevations – RR 1.24, p=0.88). A stratification, subgroup analysis was conducted which included the effects of cirrhosis, IL28B genotype variants, treatment-experienced, resistance associated substitutions (RASs), or HIV co-infection on SVR. Patients with HCV genotype 1a and 1b achieved SVR rates of 95.7% and 98.4%, respectively. Furthermore, 95.7% and 97.2% SVR rates occurred in cirrhotic versus non-cirrhotic patients on grazoprevir/elbasvir, and in 97.4% and 95.3% in treatment-naïve versus treatment-experienced, respectively. Those with IL28B CC genotype achieved an SVR rate of 97.2% compared with 96.2% of those with a non-CC genotype, while those with NS3A RAS achieved 95.9%, and 87.4% achieved SVR in those with NS5A RAS. Lastly 96.6% of mono-infected and 94.1% of co-infected patients achieved SVR. Overall, the addition of RBV did not add significant benefit, but the combination of grazoprevir/elbasvir was found to be safe and effective in patients with HCV genotype 1 infection, even in those with RASs.

Liao et al[284] conducted an analysis in 2017 involving 994 liver transplant patients who had HCV infection that were treated with LDV/SOF±RBV for 8, 12, or 24 weeks. Twelve studies were included, which were both prospective and retrospective in design. Most of the included patients were Caucasian, male, ~60 years old, had genotype 1 infection and were receiving tacrolimus as immunosuppressive therapy. The outcomes of interest with virological response, duration of treatment, use of RBV, degree of liver fibrosis, and safety. A cumulative SVR rate for all patients both with and without RBV was 96.3%. Of note, there were no difference observed in comparing retrospective and prospective study designs (both 94.6%, p=0.97). There was no difference in 12 or 24-week regimens (p=0.18) and the addition of RBV did not increase SVR rates (p=0.92). In assessment of varying degrees of liver cirrhosis, there was a higher trend in SVR in patients with no cirrhosis than in those with cirrhosis (p<0.05). In those taking RBV, 17.1% (83/484) discontinued due to AEs, while 2% (11/530) discontinued on LDV/SOF alone. The most common AE reported that was more common with RBV patients was anemia (41.9% - 203/484). Other common AEs include fatigue (39.1% - 207/530), headache (24.2% - 128/530), nausea (21.9% - 106/484), and diarrhea (19% - 92/484). In both treatment groups, 17% (90/530) experienced serious side effects, which were primarily hepatic based in nature. None of the deaths during the study period (n=15) were deemed treatment related. The authors concluded that LDV/SOF-based treatments were highly effective and safe in patients with a history of liver transplant; however, there are a limited number of studies available, so more clinical trials are necessary to valid these results.

In 2018, Ferreira et al[291] conducted a systematic review and meta-analysis of observational cohort studies to evaluate the clinical effectiveness and safety of interferon (IFN)-free therapies for HCV. The SVR at 12 weeks after the end of treatment (SVR12) was the primary outcome. Overall and subgroup meta-analyses of clinical conditions (including coinfection with HIV, cirrhosis, liver transplant, specific genotypes, and other conditions) were performed. 68 studies including 24,151 patients were included for analysis. Six treatment regimens were evaluated: SOF/LDV, SOF/DCV, SOF/SMV, DCV/ ASV, PTV/r/OBV/DSV, and SOF/RBV. The overall analysis showed SVR rates of 88-96% for all treatments except SOF/RBV which had SVR rates of approximately 80%. In general, lower SVR rates were seen in patients with treatment experience, cirrhosis, HIV/HCV coinfection, and genotype 3. The authors concluded that the second generation DAAs show promising results for effectiveness and that the best treatment decision should take into account the patient's condition and characteristics such as genotype and stage of cirrhosis.

The following table represents data from additional head to head comparative trials and other trials of interest.

After a careful review of the literature, the articles included in this therapeutic class review are not all inclusive. Key and pivotal studies that suggest one therapy is superior to another or a place in therapy of a specific product are included. Studies of low levels of evidence may not have been included in the review. Studies deemed of little relevance may also be excluded.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Interferon alfa						
Ho et al[35] 2011 **LOE 2**	Randomized, open label, multicenter Group A: interferon alfacon 1 (CINF) 15mcg/d SQ + ribavirin 1-1.2g/day x 52wks Vs Group B: Interferon alfacon 1 (CINF) 15mcg/d SQ + ribavirin 1-1.2g/day continued for 48weeks after first drop in viral load by >2log	N=64 Min 58wks Max 72wks	-Patients aged 18-65 with HCV genotype 1 and a liver biopsy w/in 5ys with evidence of chronic hepatitis	-Efficacy of CIFN -Rapid virologic response (RVR): viral negativity at week 4; Early virologic response (EVR): ≥2log decrease in viral load or viral negativity at 12wks; End treatment response (ETR): Viral negativity at end of therapy Late virologic response (LVR): viral negativity occurring between week 12 and 24	-Pooled analysis of groups A and B to evaluate efficacy of CIFN was conducted. - 31% of patients achieved an RVR at 4wks. - 20% were EVR between 8 and 12 weeks - 14% were LVR between 12 and 24 weeks - Final SVR rate was 33%. -There were no significant differences in viral negativity between group A and group B (36% vs 48%). -SVR rates were similar between group A (33%) and group B (32%). - SVR rates in patients who received 80% of planned doses and took medication 80% of the time (80/80/80) had an overall SVR rate of 85%. Univariate analysis revealed (80/80/80) patients had significantly higher SVR rates compared to those that were not compliant (p<0.05)	- Patients that adhered to 80% of the doses for 80% of the duration of the study achieved an SVR of 85%. There was a frequent early discontinuation from the study before 52 weeks due to non-compliance or side effects **CHC Comments:** - A limitation of this study is the small N, and results show potential bias due to limited sample size. Group A discontinued therapy if there was <2log decrease in viral load at 12wks. Group A and B discontinued if pt was not

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					- 61% of patients required CIFN dose reduction and 41% required ribavirin dose reduction due to adverse effects. - A significant number of patients discontinued the study prior to 52 weeks.	negative by PCR at 24wks.
Nevens et al[66] 2010 **LOE 2**	Prospective, randomized, open label multicenter **Group A:** peg-interferon 2a 180mcg QW (PEG-INF 2a) + ribavirin 1000-1200mg Vs **Group B:** interferon alfa2a 6MIU TIW + ribavirin 1000-1200 mg	N=443 48 weeks or 24 weeks if genotype 2/3	-Patients aged >18 with chronic hepatitis C who are naïve to therapy or had a previous relapse. Relapsers must have achieved an undetectable viral load and have normal ALT levels during therapy	-Sustained virologic response (SVR) rate 24 weeks after therapy. Secondary: - Sustained biochemical response rate - Proportion of patients with undetectable HCV RNA at 12, 24, 48weeks - Adverse events	-Group A achieved a significantly greater proportion of SVR (52%) compared to group B (27%; p<0.001). -There was no significant difference in SVR rates in naïve patients and relapsers in group A (54.5% vs 42.9% respectively). -SVR rates were higher in the group A relapsers (42.9%) versus group B relapsers (26.9%) but this was not significant (OR 2.13, 95% CI 0.89-5.06) -SVR rates for treatment naïve patients were higher in group A vs group B for genotype 1, 2 and 3. - Genotype 1: OR 4.4; 95% CI 2.26-7.94, p=<0.001 - Genotype 2/3: OR 3.3; 95% CI: 1.37-7.94, p=0.01	-Peginterferon alpha 2a is superior to interferon alpha, is effective in treating genotypes 2 and 3, and is effective in treating both treatment naïve and relapsed patients.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-Sustained biochemical response rates were 53% vs 34% in groups A and B respectively (p<0.001). -Patients with undetectable viral loads at 12, 24 and 48 weeks were 70%, 84%, and 85% in group A versus 42%, 52%, 73% respectively. -Adverse events occurred in 30.9% of patients in group A and 55.9% of patients in group B. There were no differences in treatment emergent adverse events between the two groups.	
Peginterferon 2a, 2b, or 2a Vs 2b						
Deterding et al[86] 2013 **LOE-2**	Randomized non-inferiority trial, Phase 3, open-label, multicenter **Group A-immediate** (symptoms): Peg-INFα-2b (1.5µg/kg) Vs **Group B-delayed** (symptoms): Peg-INFα-2b (1.5µg/kg) + RBV (>10.6mg/kg) Vs	N = 132 24 weeks	- Ages 18 years and older with acute hepatitis C, but no HIV or hepatitis B co-infection	-Sustained virologic response (SVR), HCV RNA negativity at week 24 after completion of therapy - Alanine aminotransferase concentrations - Severity & frequency of adverse events	SVR: - 67% of the symptomatic receiving immediate treatment & 54% of the symptomatic receiving delayed treatment, had SVR (difference 13.7%, 95% CI -4.6 to 32; p= 0.071). This was not statistically significantly different. - 72% of the asymptomatic patients had SVR. - 42% receiving delayed treatment did not follow-up compared to	- Delayed treatment is effective although not of equal efficacy to immediate treatment; coupled with spontaneous clearance it can reduce unnecessary treatment in closely monitored populations.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	Group C- immediate (a-symptomatic): Peg-INFα-2b (1.5µg/kg)			-Analysis of responses to the respective treatment approaches according to severity of symptoms (symptomatic vs. asymptomatic hepatitis C)	25% symptomatic or asymptomatic receiving immediate treatment. - 21% receiving delayed treatment had spontaneous HCV clearance. - 14 patients who received delayed treatment & completed treatment/follow-up achieved SVR. - 98% had a biochemical response with normal alanine aminotransferase concentrations at follow-up week 24 in group A, as did 93% of patients at observation week 60 or 24 weeks following after treatment in group B.	- Immediate treatment seems preferable in populations where loss to follow-up is great.
Flori et al[87] 2013 **LOE 1b**	Systematic review, meta analysis of randomized (RCT) and non-randomized clinical studies (NRCS) PEG-IFN α-2a (180µg/ wk) + RBV Vs PEG-IFN α-2b (1-1.5µg/kg/ wk) + RBV	N = 18,260 Duration not specified	- Adults with HCV treatment-naïve and/or treatment-experienced	- Frequency of sustained virologic response (SVR) in all genotypes - Frequency of adverse events leading to treatment discontinuation	*SVR in RCT:* -SVR was significantly higher for patients treated with PEG-IFN α-2a than for PEG-IFN α-2b for genotypes 1 and 4 [OR, 1.45; 95% CI, 1.09-2.06; p = 0.013] and for all genotypes (OR, 1.34; 95% CI, 1.05-1.72; p = 0.02). *SVR in RCT & NRCS:* - SVR was significantly higher for	-Evidence suggests that PEG-IFN α-2a and ribavirin is associated with a higher SVR than PEG-IFN α-2b and ribavirin in patient's mono-infected with hepatitis C, particularly for

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					PEG-IFN α-2a than for PEG-IFN α-2b for all genotypes (OR, 1.24; 95% CI, 1.10- 1.40; p < 0.001) - For genotypes 1 and 4 (OR, 1.25; 95% CI, 1.14- 1.36; p< 0.001) - For genotypes 2 and 3 (OR, 1.15; 95% CI, 0.98- 1.35; p = 0.08). *Adverse Drug Event in RCTs:* - 10.4% for PEG-IFN α-2a and 10.2% for PEG-IFN α-2b (OR, 0.98; 95% CI, 0.67-1.43; p = 0.92). *Adverse Drug Event in RCT & NRCS:* - Frequency similar in both groups - 11.2% for the PEG-IFN α-2a group and 10.2% for the PEG-IFN α-2b group (OR, 1.17; 95% CI, 0.98-1.38; p = 0.08).	genotypes 1 and 4. **CHC Comments:** These results may not reflect everyday practice: -Dosage variation of PEG-IFN α-2b (1.5µg/ kg/ wk usually used) - Only preliminary results (SVR at 12 weeks) of one trial were included (loss of 212 patients) - Inclusion of a trial including patients infected with HIV is a confounding factor
Katz et al[93] 2012 **LOE-2**	Meta-analysis of randomized control trials extended PEG-INF + ribavirin (x72 weeks) Vs standard PEG-INF + ribavirin (x48 weeks)	N = 1,369 72 weeks	-Patients infected with hepatitis C virus genotype 1 who had slow antiviral response	-Overall mortality, HCV-related mortality, and liver-related morbidity - Sustained virologic response (SVR) - End of treatment response (EOR) - Rate of relapse	-Overall mortality, HCV-related mortality, and liver-related morbidity were not reported in any other trials. - Sustained virological response increased in the x72 week group (71/217 (32.7%) versus 52/194 (26.8%); risk ratio (RR) 1.43, 95% confidence interval (CI) 1.07 to	- After extension of treatment from 48 weeks to 72 weeks, there was a higher proportion of SVR. There was no reporting on mortality and reporting on clinical outcomes and

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
				- Treatment adherence - Adverse events	1.92, P = 0.02, I2 = 8%; and 265/499 (53.1%) versus 207/496 (41.7%); RR 1.27, 95% CI 1.07 to 1.50, P=0.006, I2 = 38%), with a risk difference of 0.11 and calculated number needed to treat of nine. - The number of participants who had virologic relapse was found to be lower in the groups that had been treated for 72 weeks using both definitions (27/84 (32.1%) versus 46/91 (50.5%); RR 0.59, 95% CI 0.40 to 0.86, P = 0.007, I2 = 18%, 3 trials; and 85/350 (24.3%) versus 146/353 (41.4%); RR 0.59, 95% CI 0.47, 0.73, P < 0.000001, I2 =0%, 3 trials). The length of treatment did not significantly affect the adherence (247/279 (88.5%) versus 252/274 (92.0%); RR 0.95, 95% CI 0.84 to 1.07, P = 0.42, I2 = 69%, 3 trials).	adverse events were insufficient. More data are needed to recommend or reject the policy of extending the treatment period for slow responders **CHC Comments:** NNT: 9 Limitations include that all trials used SVR as primary outcome, not morbidity/mortality , and all trials were unblinded.
Minami et al[94] 2013 **LOE- 1a**	Meta-analysis, randomized controlled trials PEG-IFN α-2a + RBV Vs PEG-IFN α-2b + RBV	N = 27, 569 8-72 weeks	-Patients with chronic hepatitis C infection	-Mortality - Serious adverse events (SAE)	- All-cause and treatment-related deaths were observed in 50 (0.18%; 95% CI, 0.13- 0.24%) and 16 (0.058%; 95% CI, 0.033-0.094%) patients, respectively. -The crude SAE rate was 7.08%	- The mortality rate during PEG-INF/RBV therapy was acceptably low, but the rate of SAE was not negligible in a

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					(95% CI, 6.75- 7.41%). -The subgroup analysis revealed higher SAE rates in patients receiving PEG-IFN α-2a than in those with PEG-IFN α-2b (7.45 vs. 6.74%), and higher SAE rates with higher doses than with lower doses in PEG-IFN α-2a and 2b (11.94 vs. 6.99%, 7.10 vs. 5.05%, respectively), and with extended duration (>48 wks) than with standard duration (48 wks) (15.5 vs. 6.67%) in PEG-IFN α-2a.	treatment for a benign disease, and the rate was affected by treatment regimens.
Karabay et al[95] 2012 **LOE-2**	Retrospective, multi-center PEG-IFN α-2a (180µg/wk) Vs PEG-IFN α-2b (1.5µg/kg/wk)	N = 155 48 weeks	- Ages 18-65 years, Hepatitis B surface antigen (HBsAg) positive for more than 6 mos and those who had been HBe antigen-negative (HBe-neg) chronic hepatitis B (CHB); BMI less than 30	- Biochemical response, ALT normalization - Primary nonresponse - Virological nonresponse - Serological response - Virological response - Sustained virological response (SVR), HBV DNA level less than 2000 HBV DNA at week 72	- Treatment success was found to be 17.2% for the PEG-IFN α-2a group and 18% for the PEG-IFN α-2b group (P>0.05). - In terms of efficacy there were no significant difference between the groups (P>0.05).	- According to the results, for HBe antigen-negative CHB cases, the response rate during the sixth month after the treatment with PEG-IFN was determined to be ~17%. No difference was found between the efficacy rates of the two PEG-IFN products used I treatment.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						CHC Comments: Limitations: - Retrospective design - Higher histological index (HAI) in liver biopsies of the PEG-IFN α-2a group
Santantonio et al[112] 2014 **LOE-2**	Randomized, open-label, multicenter trial PEG-IFN α-2b 1.5mcg/kg/wkx24W Vs PEG-IFN α-2b 1.5mcg/kg/wkx12W Vs PEG-IFN α-2b 1.5mcg/kg/wk and ribavirin 10.6mg/kg/d x 12 weeks	N=133 Six-month post treatment follow-up	-Adults (18-65 years) with new diagnosis of HCV who were still viremic after 12 weeks of observation	-Undetectable HCV RNA at six months post treatment. -Secondary outcomes included virologic response at 2 wks, 4 wks, and end-of-treatment. -ALT level at the end of treatment and 6- and 12-months post-treatment.	- The response at six months was 70.5% for PEG-IFN x24 weeks (31/44), 72.1% for PEG-IFN x12 weeks (31/43) and 72.1% for PEG-IFN plus ribavirin for 12 weeks (31/43). - A rapid virological response at week 4 was achieved by 31/44 (70.5%), 37/43 (86%), 34/43 (79.1%) respectively. At the end of treatment, 34/44 (77.3%), 40/43 (93%), and 38/43 (88.4%) showed undetectable HCV RNA, respectively. -In patients treated with a 24-week course of PEG-IFN, ALT normalization was achieved by 63.6% at the end of treatment period, and 70.5% after the 6-month follow-up period.	-Response rates in this study were not influenced by combination therapy (PEG-IFN and ribavirin) or by length of therapy (3 months versus 6 months).

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					- In patients treated with a 12-week course of PEG-IFN alone or in combination with ribavirin, the ALT normalization was achieved by 72.1% and 74.4% of patients at the end of treatment, and by 62.8% and 65.1% of patients at 6-month follow-up period, respectively.	
Sato et al[154] 2014 **LOE -2**	Retrospective, multicenter, database analysis PEG-IFN alfa-2a Vs PEG-IFN alfa-2b	N = 12,706 Duration not defined	- Japanese adults with chronic hepatitis C who were treated with PEG-IFN alfa-2a or alfa-2b in combination with ribavirin	- SVR rate	- PEG-IFN alfa-2b group achieved a 62.0% SVR rate compared to 55.1% SVR rate in the PEG-iFN alfa-2a group (crude odds ratio = 1.31; 95% CI 1.23 – 1.44) however no significant difference noted when adjusted for confounders (adjusted odds ratio = 0.96; 95% CI 0.88-1.05) - Similar rates of adverse effects were noted between the two groups	- There are no noted significant differences in adult Japanese patients with HCV infection when treated with either PEG-IFN alfa-2a or alfa-2b. **CHC Comment:** Observational analysis not powered statistically to detect a true difference between treatment groups. Multiple confounders were present including

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						differences in HCV RNA analysis, physician reporting, and differences in treatment duration.
Peg-INF alfa-2a vs Peg-INF alfa 2b Treatment Naïve:						
Escudero et al[15] 2008	Non-randomized open-label study peginterferon alfa-2a SC 180µg weekly + ribavirin PO 800-1200 QD Vs peginterferon alfa-2b SC 1.5µg/kg weekly + ribavirin PO 800-1200 QD	N=183 24 or 48 weeks, depending upon HCV genotype, plus additional 24-week follow-up	- Patients 23-64 years of age, undergoing initial treatment for chronic HCV	-Proportion of patients with SVR, defined as undetectable HCV RNA in serum 24 weeks after completion of therapy - Rapid virological response and undetectable HCV RNA levels at week 4, AND early virological response and transient virological response (reappearance of HCV RNA during follow up) -adverse events causing	- Sustained virological response was similar in PEG-IFN alfa-2a and PEG-IFN alfa-2b (65.9% vs. 62%, p = 0.64), without differences according to genotype. In 117 patients with HCV genotype 1, the corresponding rates were 50.8% versus 46.6% (p = 0.713). - Rapid virological response at 4 weeks, early virological response at 12 weeks and transient virological response were also similar. - The rate of withdrawals due to treatment-related adverse events was 13.2% in the group of PEG-IFN alfa-2a and 10.9% in the group of PEG-IFN alfa-2b. Dose modification of PEG-IFN was necessary in eight patients given PEG-IFN alfa-2a and in seven given	- The two PEG-IFN plus ribavirin have comparable anti-HCV activity as shown by similar percentages of patients with sustained virological response.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
				discontinuation of treatment	PEG-IFN alfa-2b.	
Di Bisceglie et al[17] 2007	Prospective, randomized, open-label trial peginterferon alfa-2a SC 180µg weekly + ribavirin PO 1000-1200mg QD Vs peginterferon alfa-2b SC 1.5µg/kg weekly + ribavirin PO 1000-1200mg QD	N=380 12 weeks	-Treatment-naïve patients ≥ 18 years of age with serologic confirmation of high viral load, genotype 1 chronic HCV infection	- Change from baseline in log viral load at week 12. - Proportion of patients who achieved EVR (2-log drop or undetectable HCV at weeks 4, 8 and 12); proportion of patients with undetectable HCV RNA at weeks 4, 8 and 12. - Incidence of adverse events	- No observed between-group differences in viral load reduction over time - No differences in proportion of patients treated with peginterferon alfa-2a or peginterferon alfa-2b plus ribavirin who achieved EVR (66%vs 63%). Serum levels of interferon were more frequently below the level of quantitation in patients treated with peginterferon alfa-2b plus ribavirin (58-68%) than in those treated with peginterferon alfa-2a plus ribavirin (1-2%). - Patients treated with peginterferon alfa-2b plus ribavirin had higher rates of discontinuation for safety reasons (6% vs. 1%).	- A substantial percentage of patients infected with HCV genotype 1 and high viral load can achieve EVR when treated with peginterferon and ribavirin. The 2 pegylated interferons showed comparable anti-HCV activity during the first 12 weeks of treatment when combined with the same doses of ribavirin, but discontinuations for safety reasons were higher in the patients treated with peginterferon alfa-2b plus ribavirin.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
McHutchison et al[19] 2009	Double-blind (peginterferon alfa-2 dose only) multicenter, randomized controlled trial peginterferon alfa-2b SC 1.5µg/kg weekly, + ribavirin 800- 1400mg QD Vs peginterferon alfa-2b SC 1.0µg/kg weekly, plus ribavirin 800-1400mg QD Vs peginterferon alfa-2a SC 180µg weekly, + ribavirin 1000-1200mg QD	N=3070 48 weeks (24 weeks, with 24-week followup)	-Treatment-naïve patients ≥ 18 years of age with compensated liver disease due to chronic HCV genotype 1 infection and a detectable plasma HCV RNA level	- Proportion of patients who achieved EVR (2-log drop or undetectable HCV at weeks 4 and 12); proportion of patients with SVR at week 48 - Assessment of adverse events	- SVR rates were similar among the regimens: standard-dose peginterferon alfa-2b, 39.8%; low-dose peginterferon alfa-2b, 38.0%; peginterferon alfa-2a, 40.9% (p = 0.20 for standard vs. low-dose peginterferon alfa-2b; *p* = 0.57 for standard-dose peginterferon alfa-2b vs. peginterferon alfa-2a). - Estimated differences in response rates were: 1.8% (95% CI, −2.3 to 6.0) between standard- and low-dose peginterferon alfa-2b; −1.1% (95% CI, −5.3 to 3.0) between standard-dose peginterferon alfa-2b and peginterferon alfa-2a. - Relapse rates were: 23.5% (95% CI, 19.9 to 27.2) for standard-dose peginterferon alfa-2b; 20.0% (95% CI, 16.4 to 23.6) for low dose peginterferon alfa-2b; 31.5% (95% CI, 27.9 to 35.2) for peginterferon alfa-2a.	- In patients infected with HCV genotype 1, the rates of sustained virologic response and tolerability did not differ significantly between the two available peginterferon ribavirin regimens or between the 2 doses of peginterferon alfa-2b.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					- The safety profile was similar among the three groups; serious adverse events were observed in 8.6 to 11.7% of patients. Among the patients with undetectable HCV RNA levels at treatment weeks 4 and 12, a sustained virologic response was achieved in 86.2% and 78.7%, respectively.	
Ascione et al[20] 2009	Prospective, randomized, open-label trial peginterferon alfa-2a SC 180µg weekly + ribavirin PO 1000-1200mg QD (Group A) Vs peginterferon alfa-2b SC 1.5µg/kg weekly + ribavirin PO 1000-1200mg QD (Group B)	N=320 24 or 48W depending upon HCV genotype, plus additional 24-week follow-up	-Treatment-naïve patients ≥ 18 years of age with serologic confirmation of high viral load, genotype 1-4 chronic HCV infection	-Proportion of patients with SVR, defined as undetectable HCV RNA in serum 24 weeks after completion of therapy - Incidence of adverse events	- More patients in group A than B achieved an SVR (68.8% vs 54.4%; *p*=0.008). - Higher SVR rates were obtained in groups A than B among patients with -genotype 1/4 infection (54.8% vs 39.8%; *p*=0.04); -genotype 2/3 infection (88.1% vs 74.6%; *p*=0.046); -without cirrhosis (75.6% vs 55.9%; p=0.005); -with baseline levels of HCV-RNA >500,000 IU/mL (69% vs 46.2%; *p*=0.002). - SVR rates in groups A and B were not statistically different among patients with -baseline HCV-RNA ≤ 500,000 IU/mL (68.4% vs 65.7%; p=0.727);	- In patients with chronic HCV infection, treatment with peginterferon alfa-2a plus ribavirin produced a significantly higher SVR rate than treatment with peginterferon alfa-2b plus ribavirin.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-patients with cirrhosis (42.4% vs 46.1%; p=0.774). - Only 30/320 patients experienced no adverse events, with no difference between groups.	
Rumi et al[21] 2009	Open-label, randomized trial peginterferon alfa-2a SC 180 mcg weekly, + ribavirin PO 1000-1200mg QD Vs peginterferon alfa-2b 1.5 µg/kg weekly, + ribavirin PO 800-1200mg QD	N=447 48 weeks (24 weeks, with 24-week followup)	- Treatment-naïve patients 18-70 years of age with serologic confirmation of high viral load, genotype 1-4 chronic HCV infection, and a diagnostic liver biopsy done in the previous 24 months	- Proportion of patients who achieved EVR (2-log drop or undetectable HCV at weeks 4 and 12); proportion of patients with SVR at week 48 - Assessment of adverse events	- Overall, SVR rate was higher in peginterferon alfa-2a group than in peginterferon alfa-2b group (66% vs 54%, p=0.02), being 48% vs 32% in the 222 HCV 1-4 (p=0.02) and 96% vs 82% in the 143 HCV-2 (p=0.01). - The two groups showed similar rates of treatment related serious adverse events (1% vs 1%) and dropout rates for side effects (7% vs 6%). - Peginterferon alfa-2b was associated with lower rates of anemia (9% vs 23%) and higher rates of depression (31% vs 22%) than peginterferon alfa-2a, suggesting that differences might exist in safety and tolerability between treatments.	- The peginterferon alfa-2a based treatment yielded significantly more SVR than peginterferon alfa-2b.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Giannini et al[22] 2010	Trial extension (choice of study drug left to discretion of clinician) peginterferon alfa-2a SC 1.5µg/kg weekly + ribavirin PO 800-1200 QD or peginterferon alfa-2b SC 180µg weekly	N=231 3.1-5 years	-Patients with chronic HCV	-Proportion of patients maintaining SVR at time points during and at end of follow-up	-SVR was maintained in 211 patients (91%) while HCV-RNA became positive in two patients (< 1%) within 1 year after SVR; in 18 patients (8%) serum HCV-RNA was transiently positive in at least one follow-up evaluation. Clinical outcome was not significantly different between patients with persistently negative and transiently positive serum HCV-RNA.	- Sustained virological response to peg-interferon and ribavirin was maintained in 99% of patients during long-term follow-up. Late virological relapse occurred within 1 year after SVR; from a clinical perspective, patients can be considered cured of infection after this period.
Buti et al[36] 2010 **LOE 2**	Randomized prospective open label multicenter	N=1428 159 slow responders randomized to group A or B, 816 attained cEVR and were in group C.	-Aged 18-70y treatment naïve patients with liver biopsy within 18 months that confirmed chronic hepatitis.	-% patients achieving SVR -End of treatment virologic response, relapse rates, positive and negative predictive values at 8 weeks	-Patients who received treatment per protocol (n=1427) achieved an SVR of 44% in group A and 49% in group B (p=0.63) and had an overall SVR rate of 50.5% in all groups. -Patients in the intent to treat analysis had SVR rates of 43% vs 48% in groups A vs. B (p=0.64) and 80% in group C (p<0.001 versus group A). -End of treatment response was	- Weight based ribavirin + PegINF 2a therapy resulted in similar rates of SVR when used for 48wks versus 72 weeks. - The practice of extending treatment beyond 48weeks may increase cost and adverse events

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	peginterferon alfa 2b (Peg-INF) 1.5mcg/kg/wk + weight-based ribavirin 800-1400mg/day **Group A:** detectable levels at 12W & ≥2log$_{10}$ (slow responders) randomized to 48wks therapy Vs **Group B:** 72 wks Vs **Group C:** undetectable levels at 12 wks got 36W more (48wks total)	96 weeks			83%, 70% and 89% in groups A, B, and C respectively. -Relapse rates were 47% vs 33% in groups A vs B (p=0.1699). Relapse rates were significantly lower in group C (10%) compared to group A (p<0.0001) -Adherent patients who received 80% of planned dose for 80% of the duration had SVR rates of 44% and 57% in groups A and B (p=0.2). Patients who completed assigned duration of therapy had SVR rates of 46% and 57% (p=0.28) in groups A and B respectively. -Variables associated with SVR included age <40. Absence of a ≥2log$_{10}$ decline in HCV RNA at 8wks was a strong predictor of treatment failure at 48wks. Adverse events were similar across all treatment groups.	without increasing SVR rates. Extended treatment duration was associated with higher dropout rates but per protocol and completer analysis still showed no difference in SVR. **CHC Comments:** - Powered to detect superiority of 72wks to 48wks in slow responders
Lam et al[37] 2010 **LOE 2**	Randomized prospective multicenter	N= 60	-Aged 18-70yrs, treatment naïve patients with evidence of	-SVR- defined as absence of HCV RNA 6 months after completion of	- ITT analysis was used for all outcomes. -SVR was slightly lower in the 24-	- There was no statistical difference in SVR rates between 24

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	peginterferon alfa 2a 180mcg/wk (PegINF) + weight-based ribavirin 800-1200mg/dS x 24wks Vs peginterferon alfa 2a (PegINF) + ribavirin x 48 wks	72wks	chronic hepatitis on biopsy and presence of HCV genome type 6	therapy Secondary: -RVR- rapid virologic response -Complete Early Virologic Response (cEVR)- undetectable HCV RNA at 12wks -End of treatment response (ETR)- undetectable HCV RNA at end of therapy -Biochemical response Treatment adherence	week group (70%) compared to the 48 weeks (79%) but was not significant (p=0.45). -RVR was 85% in the 24wk group and 63% in the 48wk group but this difference was not significant (difference 22%, 95% CI -0.5 to 49%, p=0.12). -96% and 97% of patients achieved cEVR in the 24 and 48 wk groups respectively, (p=0.48). -ETR was similar between both groups 89% vs 94% (p=0.48). -There was no difference in normalization of ALT levels between groups. -Anemia was more frequent in the 24 wk group compared to 48wks (72% vs 44%, p=0.03) and patients in the 48wk group were more likely to receive erythropoietin.	wks and 48wks of therapy. **CHC Comments:** In this study, randomization was stratified by viral load; there was a small sample size, but first prospective study to evaluate genotype 6.
Mangia et al[38] 2010	Randomized, controlled, multicenter	N=417	-Aged 18-70yrs treatment naïve patients with HCV antibodies	-SVR rates	-SVR was achieved in 71.4% in standard therapy and 74.3% in variable therapy (p=0.58).	-Comparable SVR rates were achieved in patients who had

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
LOE- See CHC Comments	Treatment regimen: **P:** PegINF alfa 2b 1.5mcg/kg/wk **R:** ribavirin (<75kg: 1000mg/d; >75kg: 1200mg/d) *Standard:* PR x 24wks Vs *Variable:* PR x 4wks then IF: virologic response at 4wks: PRx 12W OR: No virologic response at 4wks: PR x 36W	36wks	and genotype 3 infection and elevated AST/ALT values		- There was no difference in response rates between the two groups in patients who achieved response at 4wks and those that did not. At wk 4, 63.3% of all patients had undetectable HCV RNA, 65.7% in standard tx versus 60.9% in variable therapy (p=0.36) End of treatment response was 80.7% in standard therapy vs. 88.9% in variable therapy. The difference of 8.2% was significant (p=0.028). -Of patients with End of treatment response, 12% relapsed in the standard therapy group and 16.8% relapsed in variable treatment group (p=0.22) -There was no difference in relapse rates between groups in those w/ response at 4wks and those w/o response at 4wks.	response at 4wks in standard therapy versus variable therapy. Shorter duration of antiviral therapy may be effective in patients with genotype 3. Slow responders did not differ in end of treatment responses when treated with 24 or 36wks of therapy, but sample sizes are small. Authors believe the 9.6% difference may be clinically significant. **CHC Comments:** Designed as a non-inferiority study with margin of 10% for 12/36wks vs 24wks or therapy. There was no mention of blinding so LOE could not be determined.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Kamal et al[39] 2010 **LOE 2**	Randomized prospective open label parallel group peginterferon alfa 2a 180mcg/wk (PEG-INF 2a) + RIB 1000-1200mg/d X 48 wks Vs peginterferon alfa 2b 1.5mcg/kg/wk (PEG-INF 2b) + RIB 1000mg-1200mg/d X 48wks	N=217 48 weeks	-Aged 18-60yrs interferon treatment naïve with HCV genotype 4 and elevated ALT >2x ULN w/in 6m	-SVR- undetectable viral load 24 wks after end of therapy. RVR- undetectable levels at 4wks cEVR- undetectable levels after 12wks pEVR- decrease by 2log after 12 wks ETR- undetectable at end of treatment. - Biochemical response and the Short form 36 health survey (SF-36) and Chronic liver disease questionnaire (CLDQ) were also assessed	-Overall SVR was 59.9%. PEG-INF 2a patients had significantly higher SVR rates (70.6%) compared to PEG-INF2b (54.6%), p=0.0172. - There were no differences in ETR rates (p=0.6772). - The differences in SVR were explained by differences in relapse rates (5.1% PEG-INF 2a vs. 15.7% PEG-INF 2b; p=0.0019). <u>RVR:</u> -41.3% in PEG-INF 2a vs 27.78% in PEG-INF 2b (p=0.0456). - 97.3% of patients that achieved RVR went on to achieve SVR vs those that did not (2.7%; p<0.0001). <u>cEVR:</u> -46.9% and 26.9% of those that did not achieve RVR achieved cEVR in PEG-INF 2a and 2b respectively (p=0.1213). <u>pEVR:</u> -39.1% and 30.8% had >2 log decrease in PEG-INF 2a vs 2b	- Patients with HCV genotype 4 had better SVR rates with PEG-INF 2a compared to 2b. **CHC Comments:** Analysis was ITT for all outcomes.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					respectively (p=0.3754). <u>SF-36</u>: - The physical functioning (PF) and vitality (VT) domain scores were lower in PEG-INF 2a during therapy. -Bodily pain (BP), VT, social functioning (SF), role emotional (RE) and physical component summery (PCS) scores were all higher at completion of therapy in the PEG-INF 2a group. CLDQ: -The only difference between groups was in the worry (WO) domain during therapy. - All domains except abdominal symptoms (AS) were higher in PEG-INF 2a group at completion of therapy. - Those that achieved RVR and cEVR had significantly improved CLDQ scores.	

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Sporea et al[40] 2010 **LOE 2**	Retrospective, observational multicenter pegINF alfa 2b 1.5mcg/kg/w + ribavirin Vs pegINF alfa 2a 180mcg/wk + ribavirin	N=507	-Age ≤65yrs, treatment naïve patients with HCV genotype 1 and evidence of hepatitis on liver biopsy. Patients with detectable levels at 12 weeks were declared non-responders and stopped therapy.	Efficacy: - SVR -Logistical regression for predictors of SVR	-Ribavirin dosing was based on weight <65kg 800mg/day 65-85kg: 1000 mg/d >85kg: 1200mg/day. -Of patients that remained eligible after stopped therapy for non-response, 51.9% had SVR. -Initial viral load <600,000 IU/ml, mild or no fibrosis, and age <40yrs were independent predictors of SVR. -SVR rates between PegINF 2a and PegINF 2b were similar (61.5% vs 55.6%, p=0.2129). The OR was 1.277 (95%CI 0.877-1.856).	- There was no statistically significant difference in SVR rates between patients treated with PegINF 2a vs. 2b plus ribavirin.
Wittenhoeft et al[43] 2010 **LOE 2**	Retrospective observational matched pairs cohort multicenter **Group A:** PEG-INF alfa 2a + ribavirin Vs **Group B:** PEG-INF alfa 2b + ribavirin (doses not controlled for)	N= 3414 Cohort 1: N=2378 Cohort 2: N=1672	-Cohort 1: Matched for age, HCV genotype, baseline viral load, BMI, previous therapy, presence of drug substitution, HIV co-infection.	-Virologic response -Tolerability	SVR: - Cohort 1: overall SVR was lower in group B 55.9% vs 59.9% in group A, p=0.051. - Cohort 2: overall SVR was lower in group B 54.4% vs 59.1% in group A, p=0.054. - Genotype 1 patients had significantly greater SVR in group A 49.6% vs group B 43.7%	-Response rates were similar to more controlled clinical trials. Overall SVR, EVR and EOT were significantly higher in PEG-INF 2a therapy. When matched for baseline characteristics

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			-Cohort 2: Matched for variables above and for cumulative ribavirin dose (<60%, 60-80%, >80-100%, >100%)		(p=0.047). Cohort 3: (matched for absolute ribavirin dose to account for different dose reduction regimens). - SVR was greater in group A (49.9%) versus 44.6% in group B but did not reach significance (p=0.068). -Significantly fewer patients discontinued therapy before EOT in group A compared to Group B (21.8% vs 29.6%, p<0.0001).	patients with genotype 1 had better SVR when treated with PEG-INF 2a. **CHC Comments:** Although not a controlled study, results are more likely to reflect 'real world' response rates.
Kim et al[70] 2011 **LOE- 3**	Retrospective cohort genotype 1: PEG 2a (180mcg sq QW) or PEG 2b (1.5mcg/kg sq QW) + Weight based RBV x48W Vs Non-genotype 1 cohorts: PEG 2a (180mcg sq QW) or PEG 2b (1.5mcg/kg QW) + 800mg RBV QD x 24W	N=86 23 ± 11.9 months	-Hepatitis C positive patients with detectable RNA, Child-Pugh class A, Platelets >75,000, AFP <50ng/mL and Cirrhosis based on radiologic evaluation or presence of varices	-SVR -Adverse Events	-46.7% of the population was HCV genotype 1. -Overall ETR and SVR were 55.8% and 34.9% respectively. - ETR was significantly higher in non genotype 1 patients compared to genotype 1 patients (71.1% vs 43.8%, p=0.011) - SVR was significantly higher in non genotype 1 patients compared to genotype 1 patients (52.6% vs 20.8%, p=0.002)	-Hepatitis C genotype 1 and high baseline viral load are independent factors associated with low SVR in Korean patients. **CHC Comments:** Very small in results in limited external validity. Limited discussion

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-HCV genotype 1 and high baseline viral load (HCV RNA >8x 10^5 IU/mL) were associated with lower SVR, p=0.008 and p=0.01 respectively in univariate analysis. -HCV genotype 1 and high baseline viral load were independent factors for low SVR on multivariate analysis. -5 patients stopped therapy due to adverse events. -There was no difference in rate of peginterferon dose reductions between alpha-2a and alpha-2b.	of methods- high potential for bias
Lee et al[71] 2012 **LOE- 2**	Open label randomized controlled trial PEG alfa-2a 180mcg/wk + weight-based ribavirin BID (PEG +RBV) If RVR at wk 4: PEG+RBV x 48wks vs 24wks OR, If RVR at wk 8:	N= 196 48, 60, 72, 96 weeks	-Treatment naive patients with HCV non-genotype 2 or 3, and a detectable serum HCV RNA	-SVR at 48 and 72 weeks in patients who were HCR RNA (+) at weeks 4 and 8 but achieved EVR at week 12. - SVR at weeks 24 and 48 in those with an RVR at week 4, - SVR at 36 and 48 weeks in pts that became HCV RNA (-)	-There was no statistically significant difference in SVR rates between patients with EVR randomized to 72 vs 48wks of therapy (40% vs 49%, p=0.05). -SVR rates were 84% in patients with RVR at 4-8wks who were randomized to 24 or 48 weeks of therapy. -SVR rates were not significantly different in patients with response	-Shortening therapy to 24wks in patients with a week 4 responses and to 36wks in those with response at 8 weeks resulted in similar SVR rates in a 48-week regimen. - Lengthening therapy to 72

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	PEG+RBV x 48wks vs 36wks OR, If HCV RNA (-) or ≥ 2log drop at wk 12: PEG+RBV x 48wks vs 72wks OR, If HCV RNA <2log drop, D/C therapy			between week 4 and 8.	at week 8 randomized to 36 or 48wks of therapy (73% vs 74%, p=1.0). -There was no difference in relapse rates between any of the groups. -The highest incidence of dose reductions or withdrawal for AE's was in the 72-week group. -Incidence of serious AE's was 10-17% across all groups.	weeks did not improve SVR rates
Sarrazin et al[72] 2011 **LOE- 3**	Prospective, open-label, case-control peginterferon alfa-2b 1.5mcg/kg qwk + weight-based Ribavirin x 24, 30, 36, 42, 48, 60 or 72 weeks based on response Vs traditional therapy length 48wks	N=623 (398 active cases + 225 controls) 48-96wks	-Treatment naïve HCV genotype 1 patients	-Proportion of patients with an SVR 24wks after therapy between traditional therapy (TT) length vs individualized therapy (IT) -SVR rates between traditional therapy (TT) length and individualized therapy (IT) based on first time point of undetectable HCV RNA levels	-End of treatment (ETR) response was 68% in IT compared to 64% in TT (p=0.351). -Relapse rates were 27% in IT compared with 30% in TT (p=0.516). -SVR in IT was 55% and 48% in TT which showed non-inferiority of IT compared to TT (p<0.001; 95%CI: 49.5-59.5). -Virologic nonresponse was similar in IT and TT groups 22% vs 24% respectively (p=0.523).	-Highly individualized regimens are non-inferior to standard 48wk therapy. - Individualized regimens result in high SVR in rapid responders and increased SVR in slow responders.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
				IL28B genotype presence	-13.8% of IT patients received 48wks of therapy, 28.4% received shorter durations of therapy and 32.4% received longer durations of therapy. -There was no difference in SVR rates according to baseline viral load and time of undetectable viral load. -Baseline IL28B is highly significantly correlated with SVR: CC genotypes had a 97% chance of achieving virologic response vs a 68% chance and a 54% chance for CR and TT genotypes (p<0.001).	
Choi et al[67] 2011 **LOE- 2**	Retrospective cohort peginterferon alfa-2a 180mcg/wk or peginterferon alfa-2b 1.5mcg/kg/wk + weight based ribavirin X 48wks for genotype 1 or x24 wks non genotype 1	N=292 18m	-Patients with chronic hepatitis C treated with PEG-INF and ribavirin	-SVR every 6m after end of PEG-INF +ribavirin therapy	-SVR was achieved in 75.5% of genotype 1 patients and 92.7% of genotype non-1. -224 of the 292 initial SVR patients had follow up for more than 6months. -SVR was maintained in all patients. 2 patients who achieved SVR developed Hepatocellular carcinoma during follow-up.	-There was sustained SVR in patients treated with PEG-INF at a median of 18m of followup. Intensive follow-up monitoring is not needed for patients achieving SVR.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-There was no relationship between dose and reappearance.	
Dogan et al[85] 2013 **LOE 1b**	Randomized controlled trial **Group A:** Peg-INFα-2a (180µg/wk) + RBV (1,000-1,200mg/day) Vs **Group B:** Peg-INFα-2b (1.5µ/kg) + RBV (1,000-1,200mg/day)	N = 78 48 weeks	- Ages 18 years and older with chronic HCV genotype 1 infection. With compensated liver disease and a detectable plasma HCV-RNA level and had not been treated previously for hepatitis C infection. Platelet count of ≥80,000 per mm^3, and absolute neutrophil count of ≥1,500 per mm^3, and hemoglobin level of 12g (women) or 13g (men) or more per dL.	- Sustained virologic response (SVR) - Rapid virological response (RVR) - Early virological response (EVR) -End of treatment response (ETR) -Adverse events	- SVR (46 vs. 51%) & RVR (31 vs. 26%) rates were similar for peg-INFα-2a and Peg-INFα-2b groups. - Overall SVR rate for these standard therapies was 48.7%. - Multivariate analysis showed HCV viral load was significantly associated with RVR, EVR, ETR, and SVR inversely (r= -0.25, P<0.05, and r= -0.34, r= -0.53, r= -0.42, P<0.01, respectively). -Safety and adverse-event profiles were similar between patients treated with Peg-INFα-2a and Peg-INFα-2b, in combination with the same RBV regimens	The rates of SVR did not differ significantly between the two available Peg-INF-ribavirin regimens **CHC Comments**: A limitation of this study is the small sample size.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Coppola et al[88] 2012 **LOE 1b**	Systematic review, meta-analysis of randomized (RCT) and non-randomized clinical trials PEG-IFN α-2a (180µ/wk) + RBV Vs PEG-IFN α-2b (1.5µg/kg/wk) + RBV	N = 3,026 Duration not specified	- Adults with genotype 1 chronic HCV infection - Anti-HIV-negative and treatment-naïve	- Rapid virological response (RVR), Early virological response (EVR), End of treatment response (ETR), and Sustained virologic response (SVR)	- PEG-IFN α-2a and PEG-IFN α-2b showed similar rate of RVR (RR = 1.05; 95% CI = 0.87 – 1.27, p = 0.62) & SVR (RR = 1.08; 95% CI = 0.99- 1.18, p = 0.098). - PEG-IFN α-2a more frequently than PEG-IFN α-2b achieved EVR (RR = 1.11; 95% CI= 1.02- 1.21, p= 0.013) and ETR (RR= 1.22; 95% CI= 1.14- 1.31, p < 0.0001).	- Concluded that similar SVR rates were found between the standard schedule of PEG-IFN α-2a compared to PEG-IFN α-2b, both in combination with ribavirin and therefore both treatments can be used indifferently for patients with genotype 1 chronic HCV infection who are anti-HIV-negative and naïve to antiviral treatment. **CHC Comments:** None of the studies had the observers masked to the treatment and to the results, and many studies did not describe the randomization procedure. Also,

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						the results were combined from RCT and non-randomized studies.
Tseng et al[115] 2013 **LOE-2**	Prospective, observational cohort study PEG-IFN α-2b 1 mcg/kg/wk for 24-48 wks Vs PEG-IFN α-2b 1 mcg/kg/wk and ribavirin 200 mg 3x/wk for 24-48 wks	N=52 24 to 48 weeks of treatment (48 weeks for HCV genotype 1 patients and 24 weeks for genotype non-1 patients) followed by 24 weeks of follow-up	-Adults on chronic kidney disease on hemodialysis and with chronic HCV naïve to interferon therapy	-End of treatment virologic response (undetectable HCV RNA) and sustained virologic response at 24 weeks after end of treatment. - Proportion of adverse events in each group	- Patients receiving combination therapy had a significantly higher end-of-treatment virologic response rate than did those receiving monotherapy (85% vs 62%, respectively, in ITT [p = 0.03] and 100% vs 80%, respectively, in PP (p=0.03). -Patients receiving combination therapy also had a significantly higher sustained virologic response rate than those receiving monotherapy (62% vs 27%, respectively, in ITT (p=0.01) and 73% vs 35%, respectively, in PP (p=0.01). - The most frequently observed adverse events were anemia (grade 3; 58% and 27%, respectively [p=0.03]) and thrombocytopenia (grade 3; 61.5% and 50%, respectively [p = 0.5]) in patients receiving peginterferon	-Peginterferon alfa-2b and ribavirin combination therapy in HCV treatment-naïve dialysis patients showed a higher sustained virologic response compared to peginterferon alfa-2b monotherapy; but patients who received combination therapy had a significantly higher rate of severe anemia compared with those who received monotherapy.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					alfa-2b combo vs monotherapy.	
Jin et al[118] 2013 **LOE - 2**	Retrospective, multicenter trial PEG-IFN α-2a 180 mcg/wk and ribavirin 800-1200 mg/day Vs PEG-IFN α-2b 1.5 mcg/kg/ week and ribavirin 800-1200 mg/day	N = 661 Follow-up: 24 weeks after end-of-treatment: duration in both groups was planned for 24W in patients with HCV genotype 2/3 and 48W with genotype non-2/3	Treatment-naïve Korean adults diagnosed with chronic HCV infection between January 2000 and September 2008. Patients with hepatitis B virus and HIV coinfection were excluded.	-The proportion of patients with sustained virologic response (SVR; undetectable HCV RNA) at 24 weeks after end-of-treatment. -Rapid virological response (RVR) and end of- treatment response (ETR) were defined as HCV RNA negative at treatment week 4 and at the end of treatment, respectively. -Safety	- By intention-to-treat analysis, in 416 patients with genotype 1, ETR (69.7% vs. 74.7%, P=0.32) and SVR (62.2% vs. 64.2%, p=0.76) were not different between the two PEG-IFN groups. In 235 patients with genotype 2/3, ETR (82.3% vs. 85.1%, p=0.59), and SVR (79.4% vs. 79.8%, p=1.00) were not different between two PEG-IFN groups. RVR rates were not different between two PEG-IFN groups in patients with genotype 1 (61.0% vs. 51.9%, p=0.41) and genotype 2/3 (66.7% vs. 82.4%, p=0.21). - The rates of common AEs in the two groups, that is GI symptoms, dermatologic symptoms, and emotional friability were not significantly different (p-values for each >0.05). -Although the rates of flu-like symptoms or alopecia showed statistical difference between two PEG-IFN groups (P<0.01), the number of patients with grade 3	-RVR, ETR, SVR, and the safety of PEG-IFN α-2a were not different with those of PEG-IFN α-2b in treatment-naive Korean patients with chronic HCV, regardless of HCV genotype. However, the design of this trial was retrospective and further research is needed to validate these results.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					was small in each group.	
Fernandez-Rodriguez et al[123] 2014 **LOE - 2**	Randomized, multicenter, open-label trial PEG-IFN α-2a 180mcg & RIB 800mg/day x 24W Vs PEG-IFN α-2a 180mcg plus RIB 800mg-1.6g/day & epoetin 400 IU/kg/wk x24 weeks	N = 97 Follow-up: 24 weeks after complete treatment	-Adults with chronic, treatment-naïve HCV infection and genotype 3.	-The SVR rate, defined as the undetectable serum HCV RNA level 24 weeks after completion of treatment. -Secondary outcomes included the RVR, defined as an undetectable serum HCV RNA level at week 4 of treatment, and safety variables including blood tests and adverse events.	- The SVR rate by ITT analysis was 64.3% in the low-dose ribavirin arm and 61.8% in the high-dose arm (p=0.835. In the PP analysis, 85 subjects who completed the protocol with no missing outcomes were included, 35 in the low-dose arm and 50 in high-dose arm. The respective SVR rate was 77.1% and 68% in each arm (p=0.464). - RVR was achieved by 69 out of 97 patients (71.1%). In low-dose ribavirin arm, the RVR rate was 64.3% versus 76.4% in the high-dose ribavirin arm (p=0.259). - There were only two cases of mild anemia in the low-dose arm and two cases in the high-dose arm. The rate of serious adverse events was low (*n* = 3), with 2 cases of neutropenia and 1 case of oral aphthae. Among the overall adverse events, fatigue was the most frequently reported.	-Overall results showed that treatment with high dose RBV combined with peginterferon was not more effective than standard treatment in patients with HCV genotype 3. Nevertheless, this treatment was safe when particular care was taken to prevent anemia. Further studies on the treatment of infection with HCV genotype 3 are needed.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Berak et al[155] 2014 **LOE-2**	Prospective, randomized, single center, open-label, comparison study PEG-IFN alfa-2a 180ug/week plus ribavirin Vs PEG-IFN alfa-2b 1.5ug/kg/week plus ribavirin	N = 212 48 weeks	- Adult patients with chronic HCV genotype 1 infection who were treatment naïve and without any history of decompensated liver disease	- Proportion of patients achieving SVR24 (HCV RNA <50 IU/mL) 24 weeks after the end of treatment	- 50/101 (49.5%) of patients receiving PEG-IFN alfa-2a and 49/111 (44.1%) of patients receiving PEG-IFN alfa-2b achieved SVR24 (p = 0.43). - No significant differences observed between treatment arms when patients were stratified according to pre-treatment viral load, age, BMI, and liver fibrosis. - 50.5% of patients receiving PEG-IFN alfa-2a required dose reduction and 33.3% required dose reduction in the PEG-IFN alfa-2b group.	- In adult patients with HCV genotype 1 infection who are treatment naïve, there are no noted differences in efficacy when receiving either PEG-IFN alfa-2a or PEG-IFN alfa-2b.
Peg-INF alfa-2a or Peg-INF alfa 2b Non-responders, difficult to treat, relapsed:						
Scotto et al[14] 2008	Randomized open-label study peginterferon alfa-2a SC 180µg weekly + ribavirin PO 15mg/kg QD Vs peginterferon alfa-2b SC 1.5µg/kg QW + ribavirin 15mg/kg QD	N=108 12 weeks, with follow-up continuation to 48 weeks upon attainment of non-detectable hepatitis C virus (HCV)	- Patients with well compensated chronic HCV, non-responding to previous antiviral treatment	- Incidence of early and sustained virological response (EVR and SVR), at 12 and 48 weeks respectively -Adverse events	- After 12 weeks of treatment, viral load reduction was >2 $\log_{10}$ with both peginterferon alfa-2a (-2.53) and peginterferon alfa-2b (-2.48) with no significant difference. - At the end of week 48, HCV RNA was undetectable in 14 of 54 patients (25.9%) receiving peginterferon alfa-2a and in 15 of 54 patients (27.7%) receiving	- In chronic hepatitis C patients who were non-responsive to previous therapy, EVR to the two pegylated interferons did not significantly differ with a similar therapeutic efficacy

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
		RNA			peginterferon alfa-2b. - When terminating follow-up, an SVR was observed in 11 of 54 patients (20.4%) who received peginterferon alfa-2a and 10 of 54 patients (18.4%) receiving peginterferon alfa-2b. - The incidence and severity of adverse events was similar in both groups.	defined as SVR.
Special Populations:						
Huang et al [44] 2011 **LOE 2**	Prospective, open label, multicenter case-control HCC cohort Vs No HCC at enrollment. All received: PEG-INF 2a 180mcg/wk + ribavirin <75kg: 1000/d >75kg: 1200mg/d	N=169 X 24 weeks if Genotype 2, 3 X 48wks if Genotype 1	-Taiwanese HVC patients >18yrs with evidence of chronic hepatitis on biopsy HCC Group: very early or early stages of Hepatocellular carcinoma (HCC)	- Sustained virologic response - Rapid virologic response (RVR)- undetectable HCV RNA levels at 4wks and end of treatment response (ETR)- undetectable levels at end of treatment were also assessed -Predictive factors for treatment response	-Baseline demographics of 80/80/80 adherence was significantly higher in the HCC group (84.1%) vs cirrhosis group (60.9%; p=0.001). -SVR was achieved in 48.5% of HCC patients and significantly higher at 64.4% in cirrhosis patients (p=0.04). -This difference was observed only in genotype 1 patients (33.3% vs 60.7%, p=0.005). -SVR was not different between HCC and cirrhosis patients that	- HCC patients treated after complete eradication of HCC have a lower SVR and higher RR compared to cirrhosis groups. Genotype 1 infection was associated with this inferiority whereas there was no difference in outcomes in genotype 2 or 3 patients.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					achieved 80/80/80 adherence (50.7% vs 64.2% respectively; p=0.12). There were no differences between genotypes in this subgroup. -There were no differences in achievement of RVR between cohorts. -There were no differences in achievement of ETR between cohorts. -HCC patients had higher relapse rates (RR) 25.6% vs 12.6% in the cirrhosis cohort, (p=0.03). - Genotype 1 patients in the HCC cohort had higher relapse rates 29.2% vs 10.7% in the cirrhosis Genotype 1 patients. (p=0.02). - Predictive factors on SVR in both groups included: RVR, baseline viral load. - There were no differences in serious ADE's.	

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Kainuma et al[52] 2010 **LOE 2**	Prospective Cohort study Group A: genotype 1, age <60y Vs Group B: genotype 1, age ≥ 60y Vs Group C: genotype 2, Age <60ys Vs Group D genotype 2, age ≥60ys	N=1251 All cohorts: PEG-INF 2b + ribavirin 600-1000mg/d X 48wks if Genotype 1, x24 wks if Genotype 2	-Any patient >18yrs old with HCV and confirmed hepatitis on biopsy.	-SVR- sustained virologic response and EOT- end of therapy response	<u>Genotype 1:</u> - EOT response was higher in group A than Group B, 72.5% vs. 45%, p<0.001. - SVR was significantly higher in group A than Group B, 47.3% vs 22.9% p<0.001 <u>Genotype 2:</u> - EOT response was not different between the groups, 94.8% vs 90.1%. - SVR was significantly higher in group C than in group D, 82.9% vs 65.5%, p=0.004. -SVR was significantly lower in Genotype 1 overall compared to genotype 2, 40.7% vs. 79.6% respectively, (p<0.001). -SVR significantly decreased with age in both genotypes. Genotype 1 patients >70y had SVR rates of 5.6-26.3% and Genotype 2 patients >70y had SVR rates of 57.1-100%. -Discontinuation rates were significantly higher in Group B	- Interferon + ribavirin therapy was effective in the older population if minimum effective doses are attained. There were a greater number of older patients that discontinued therapies in genotype 1 groups due to adverse events. **CHC Comments:** Pertinent unmatched baseline characteristics: Group B had lower BMI and lower previous INF therapy at baseline compared to Group A. Group D had lower baseline viral load compared to Group C. - There were

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					compared to Group A, but there were no differences in discontinuation between Group D and Group C.	significantly more ribavirin dose reductions in the age>60 cohorts.
Liu C et al[53] 2010 **LOE 2**	Retrospective Cohort study **Group A:** Detectable HCV RNA level after 16 wk observational period got PEG-INF 2a 135mcg/wk x 24wks **Group B:** Undetectable levels at 16W Vs historical controls **Group C:** Controls with detectable HCV levels **Group D:** Controls with undetectable levels	N=35 48 weeks	Hemodialysis patients aged 18-65 with acute hepatitis C (ALT >15x ULN)	Efficacy: - Intent to treat SVR - Rapid virologic response (RVR) - Early Virologic Response (EVR) - End of Treatment response (EOT) Safety	-88% of treated patients (Group A) had SVR and 100% of observed patients (Group B) had spontaneous HCV clearance whereas 16.7% of historical controls (Groups C+D) had spontaneous HCV clearance). -Rates of SVR were higher in group A vs Group C+D ($p<0.001$) and were higher in Group A+B vs Group C+D ($p<0.001$). -RVR: 97.1% in treated patients (Group A). -EVR: 94.3% in treated patients (Group A). -EOT: 100% of treated patients (Group A). - 5.7% of patients withdrew from the study at 8 and 10 weeks due to side effects. - 20% of patients required dose	- Acute Hepatitis C in hemodialysis patients treated early with interferon therapy can obtain a good SVR rate with a favorable side effect profile.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					reductions. - There were no serious adverse events.	
Mendez-Navarro et al[54] 2010 **LOE 2**	Randomized, prospective, open-label study **Double tx:** PEG-INF 2a 180mcg/wk + ribavirin 1000-1200mg/d x 48wks Vs **Triple tx:** PEG-INF 2a 180mcg/wk + ribavirin 1000-1200mg/d + amantadine 200mg/d x 48wks	N=124	-Latino patients aged 18-65 with HCV genotype 1 infection with elevated ALT's for at least 6m. Only Child-Pugh class A cirrhotic patients were eligible.	- Sustained virologic response (SVR) - Early Virologic response (EVR): >2log$_{10}$ decrease or undetectable HCV RNA levels at 12 weeks and End of therapy response (EOT): undetectable at end of therapy were also assessed.	-There was no significant difference between groups in SVR: 39.7% and 42.6% of patients in double and triple therapy achieved sustained virologic response respectively (p=0.561). -There was no significant difference between groups in EVR (68.2% vs 75.4% in double and triple therapy respectively, p=0.376). -There was no significant difference between groups in EOT (58.7% vs 57.3% in double and triple therapy respectively, p=0.879). -There were 38% non-responders in the double group and 42.6% in triple group. -The relapse rate was 22.3% in double tx group and 14.8% in the triple tx group.	- Triple therapy with amantadine was equivalent to double therapy in terms of tolerability but did not demonstrate benefit in rates of SVR. **CHC Comments:** This study had a small sample size and post-hoc power calculations indicate they needed more patients to detect an adequate difference. It was also a non-blinded study.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Sokal et al[55] 2010 **LOE 2**	Prospective, open label, multicenter **Group A:** (genotype 2,3) PEG-INF 2a 100mcg/m^2/w + RIB max 1200mg x24W Vs **Group B:** (genotype 1, 4,5, 6) PEG-INF 2a 100mcg/m^2 (max 180mcg) / wk + ribavirin 15mg/kg/day (max 1200mg) x 48wks	N= 65 72wks	-Aged 6-17yr, treatment naïve patients with HCV serum antibodies	-Intent to Treat SVR rate -EVR and EOT were also assessed -Safety	-SVR was maintained in 89% of Group A patient's vs 57% in Group B ($p<0.01$). -Among group B patients, those with normal basal transaminases had an 89% SVR compared to 36% SVR in those with abnormal transaminases. EVR: rates in Group A were 83% compared to 57% in Group B ($p<0.05$). Of these patients, 93% in group A and 81% in group B went on to reach SVR. EOT: rates in group A were 94% compared to 57% in group B ($p<0.000$)1 - 10 patients, all from group B, stopped treatment prematurely, 8 due to no virologic response at 24wks. - 2 withdrew due to serious ADE's. The most common ADE's included fatigue, fever/ flu like symptoms, and headache. - There was no effect on weight	- PEG-INF therapy + ribavirin were well tolerated and showed benefits for reducing SVR in a large population infected with Hep C. The response rates relative to genotype were similar in children to those seen in adults.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					loss or height growth.	
Wirth et al[56] 2010 **LOE 2**	Prospective open label multicenter Genotype 1, 4 and 3 (>600,000IU/ml baseline viral load): PEG-INF 2b 60mcg/m^2 qwk + ribavirin 15mg/kg/d (max 1200mg) x **48wks** Vs Genotype 2, 3 (<600,000 IU/ml baseline viral load): PEG-INF 2b 60mcg/m^2 qwk + ribavirin 15mg/kg/d (max 1200mg) x **24wks**	N= 107 72 weeks	-Aged 3-17y, treatment naïve patients with chronic hepatitis C	-SVR -RVR- undetectable viral load at 4 weeks, EVR- undetectable viral load at 12 weeks, and Relapse- detectable viral load after completion of treatment during follow up were also assessed	-Overall SVR was attained by 65% of patients. Genotype (G) was the main predictor of outcome. - SVR rates for G1, G2, G3 and G4 were 53%, 93%, 93% and 80% respectively - SVR rates for G1 patients were higher 72% vs 29% in those with baseline viral loads <600,000 IU/ml compared to high viral loads. (p=0.0006) - RVR and EVR were strong predictors of SVR in all genotypes -Relapse occurred only in G1 patients (12%) -ADE's were similar to those reported with INF therapy. There were no serious ADE's reported. -Dose reductions were necessary in 25% of patients due to neutropenia, weight loss, or anemia. -Weight gain and Height growth	-Overall SVR rates of 65% were attained in the pediatric population with Peg-INF 2b + ribavirin. The rates reported here are significantly higher than those reported in children treated with PEG-INF 2a + Ribavirin. Low rates of fibrosis and low baseline virologic loads in the pediatric population may explain the higher SVR rates seen in this population compared to the adult population.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					were decreased in children treated with PEG-INF but they all responded with increases in weight gain and growth after therapy completed. -Abnormal TSH levels were seen in 23% of patients.	
Schwartz et al [57] 2011 **LOE 1b**	Randomized, placebo controlled multicenter PEG-INF 2a 180mcg/1.73m^2 (max 180mgc) qwk + ribavirin 15mg/kg BID (max 1200mg/d) x48wks Vs PEG-INF 2a 180mcg/1.73m^2 (max 180mgc) qwk + placebo x 48wks	N= 114 2yr follow-up	-Aged 5-18yr, treatment naïve patients with chronic hepatitis C documented on biopsy or by inflammation.	-SVR -RVR- undetectable HCV RNA at 5wks, and EVR- >2log decrease at week 12 were also assessed Safety: - ADE's	-SVR was achieved by 53% in PEG-INF 2a + Ribavirin (RBV) vs. 21% in the PEG-INF 2a + placebo group. - Differences in HCV RNA decline were significant at 3wks and remained significant to 24wks. -RVR was achieved in 10% in PEG-INF/Placebo and 24% in PEG-INF/RBV therapy (p=0.06). -EVR was achieved in 24% in PEG-INF/Placebo and 59% in PEG-INF/RBV therapy (p<0.001). -End of Therapy response was achieved in 37% in PEG-INF/Placebo and 64% in PEG-INF/RBV therapy (p<0.007). -Influenza like, headache and GI symptoms occurred in almost all	-Addition of ribavirin to PEG-INF 2a therapy in children significantly improves SVR rates. The only exception was in children with low baseline viral loads at enrollment. **CHC Comments:** Reported ribavirin dose differs from the other 2 pediatric trials that report a dose of 15mg/kg/d. Randomization was stratified according to genotype

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					children with no difference between blinded groups. -27% required dose reduction for neutropenia, 2 children developed hypothyroidism.	
Druyts et al[89] 2013 **LOE 1b**	Systematic review, meta-analysis PEG-IFN α-2a (100µ/m^2/wk) + RBV (15-20mg/kg/day) Vs PEG-IFN α-2b (1-1.5µg/kg/wk) + RBV (15-20mg/kg/day)	N = 438 24 or 48 weeks	- Children and adolescents (3-18 years old) with confirmed HCV infection	- Sustained virologic response (SVR) - Complete early virologic response (EVR) - Discontinuation due to adverse events, viral breakthrough, lack of response, & relapse	- SVR: 58% of subjects achieved SVR (95% CI, 53%- 64%) - EVR: 70% of subjects achieved EVR (95% CI, 58%- 81%) - EVR and SVR were higher for those with HCV genotypes 2/3 than 1/4. - Discontinuation due to adverse events and viral breakthrough were each 4%, discontinuation due to lack of response was 15%, and relapse was 7%. - Anemia, neutropenia, leukopenia, and thrombocytopenia were 11%, 32%, 52%, and 5%, respectively - Alopecia, injection site erythema, and pruritus were 13%, 27%, and 10%, respectively.	- PEG-IFN/RBV combination treatment is effective and safe in treating children and adolescents with HCV. Efficacy is improved for those infected with genotypes 1/4. It is possible that minor growth inhibitions may occur with treatment, but in most cases, growth returns to normal with cessation of therapy **CHC Comments**: Small number of trials, only one RCT included

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					- Small growth inhibitions were observed during treatment	
Ogawa et al[90] 2013 **LOE 2**	Prospective, multicenter study PEG-IFN α-2b + RBV	N = 1,013 ~3.6 years	- Japanese patients (18 yrs or older) with chronic hepatitis C (HCV) infection - With no history of hepatocellular carcinoma (HCC)	- HCC incidence - Sustained virologic response (SVR) - Transient virologic response (TVR) - Non-virological response (NVR)	- 47 patients (4.6%) developed HCC during the observation period. - In the non-cirrhosis group, the 5-year cumulative incidence rates of HCC for SVR (1.7%) and TVR (3.2%) groups were significantly lower than those of the NVR group (7.6%; p= 0.003 and p= 0.03, respectively). - In the cirrhosis group, the 5-year cumulative incidence rate of HCC for SVR (18.9%) and TVR (20.8%) groups were also significantly lower than the NVR (39.4%) group (p= 0.03 and p= 0.04, respectively).	- SVR and complete viral suppression during treatment with relapse (TVR) were associated with lower risk of HCC development when compared to NVR. **CHC Comments:** - Lacks data on insulin resistance and hepatic steatosis, generalized that there are high cumulative incidence rates of HCC.
Koretz et al[91] 2013 **LOE 1a**	Meta-analysis, randomized clinical trials PEG-INF + placebo Vs PEG-INF monotherapy	N = 1,976 24 wks - 5 yrs	-Patients with chronic hepatitis C who have failed prior antiviral therapy and who have severe histologic	-Mortality, quality of life, & adverse events -Liver-related morbidity, sustained viral responses, biochemical responses, histologic	- No significant difference was observed in either all-cause mortality (9.3% versus 7.2% [RR, 1.30; 95% CI, 0.95- 1.79]), or hepatic mortality (7.7% versus 7.2% [RR, 1.07; 95% CI, 0.70-1.63]).	-The authors conclude that in this scenario retreatment with interferon did not appear to provide significant clinical benefit and, when

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			disease but compensated liver disease	improvements, and costs. Total hospital admissions	- When only the two trials at low risk of bias were combined, all-cause mortality was significantly higher in the recipients of the pegylated interferon (9.4% versus 6.7% [RR, 1.41; 95% CI, 1.02-1.96]). - There was less variceal bleeding in the interferon group (0.5% versus 2.1% [RR, 0.24; 95% CI, 0.09- 0.67]). - In one trial, the quality of like data showed the pain score was significantly worse in the interferon group. -Adverse events were common in the interferon group; include hematologic complications, infections, flu-like symptoms, and rash. -The interferon group had significantly more SVR (3.6% versus 0.2% [RR, 15.38; 95% CI, 2.93- 80.71])	only low risk of bias were considered, retreatment for several years may even have increased all-cause mortality. Treatment did result in improved SVR and histologic evidence of inflammation. Interferon monotherapy cannot be recommended for these patients. **CHC Comments:** Limitations: Number of included of trials were small (n= 7), and the 2 large trials included patients with advanced fibrosis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Protease Inhibitors/Others:						
Kwo et al[46] 2010 **LOE 2**	Randomized, multicenter open label, 2-part study **P:** peginterferon alfa 2b 1.5mcg /kg QW **R:** ribavirin 800-1400mg g/ **B:** Boceprevir 800mg TID <u>Part 1:</u> **PR48:** PR x 28wks (control grp) **PR4/PRB24:** PR x 4wks, then PRB x 24wks **PR4/PRB44:** PR x 4wks, then PRB x 44wks **PRB28:** PRB x 28wks **PRB48:** PRB x 48wks	N=520 28 to 48wks	- Aged 18-60yrs treatment naïve hepatitis C (HCV) genotype 1 patients. Liver biopsy consistent with HCV infection w/in 5yrs was required with Hgb >13mg/dL in men, >12mg/dL in women, Neutrophils >1.5 x10^9/L and platelets >100x10^9/L - Ribavirin weight based: <65kg: R 400mg BID 66-80kg: 400mg AM/ 600mg PM 81-105: 600mg BID >105kg: 600mg AM/ 800mg PM	-SVR- proportion of patients with undetectable HCV RNA (<15 IU/ml) 24wks after discontinuation of therapy -Viral breakthrough: a 2$\log_{10}$ increase in HCV RNA from nadir on 2 consecutive measurements w/a quantitative concentration of ≥50,000 IU/ml	<u>Part 1:</u> -All 4 boceprevir groups (PR4/PRB24; PR4/PRB44; PRB28; PRB48) had significantly better SVR than the PRB48 control group. - 28wk Groups vs. Control - PR4/PRB24: 56% SVR (95%CI: 46-66, p=0.05) - PRB28: 54% SVR (44-66, p=0.013) - 48wk Groups vs. Control: - PR4/PRB44: 75% SVR (65-85, p<0.0001) - PRB48: 67% SVR (57-76, p<0.0001) - 48wk groups had significantly lower relapse rates compared to control (PRB48, p=0.0079, PR4/PRB44, p=0.002) - Lead in groups vs no lead in: • Rates of breakthrough trended higher in groups with no lead in therapy (PRB28, PRB48 vs PR4/PRB24, PR4/PRB44; 4% vs. 9% respectively, p=0.057	- Addition of boceprevir to standard of care significantly increased SVR at 28 and 48weeks. Responses in the 48wk boceprevir group were significantly higher than the 28wk groups. Use of low dose ribavirin decreased ADE's but did not improve SVR compared to control. Lead in therapy had lower relapses and better SVR but did not meet significance. **CHC Comments:** Part 1 evaluated a 4-week lead in time w/ PegINF+ ribavirin vs. no lead in AND 28 weeks vs. 48 weeks of

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	Part 2: **PRB48:** PRB x 48wks (control) **Low dose PRB48:** P + Ribavirin 400-1000mg/d + B x 48wks				Part 2: - Low Dose PRB: 37% SVR (24-49) - Low Dose PRB was associated with a high relapse rate 22% vs 11% PRB48. - Response rates in black participants and patients with cirrhosis were higher in boceprevir groups compared to control. -The most common side effects in the boceprevir group were fatigue, anemia, nausea and headache, which was similar to PR48 control. - The rate of dysgeusia and anemia was higher in boceprevir groups than other groups. - Treatment discontinuation was 9-19% in boceprevir studies compared to 8% in the PR48 control group. - Epoetin was allowed in the trial (40%).	therapy. Part 2 evaluated weight based low dose versus standard dose ribavirin to determine if efficacy was maintained while reducing anemia Part 1 randomization was stratified by race and cirrhosis status controls for bias in the HCV population. Also, numbers in the multivariate analysis were small, would need larger studies to confirm these outcomes.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Poordad et al[47] 2011 **LOE: 1b**	Randomized, placebo-controlled multicenter P: peginterferon alfa 2b 1.5mcg/kg qwk R: wt based ribavirin 600-1400mg/day B: boceprevir 800mg TID **Control:** PR x 4wks then PR + placebo x 44wks Vs **Group 2:** PR x 4wks then PRB x24wks - if HCV RNA undetectable from 8-24 wks stopped - if HCV RNA levels detectable anytime from 8-24wks then PR + placebo Vs **Group 3:** PR x 4wks then PRB x 44wks	N=1,097 2 cohorts: 159 Black 940 Non-Black 72 weeks follow up	-Aged 18-60yrs treatment naïve hepatitis C (HCV) genotype 1 patients weighing 40-125kg, with HCV RNA levels ≥10,000 IU/ml	-Difference in rates of SVR between either response tx group or fixed dose group compared to control. - Sustained virologic response (SVR): undetectable HCV RNA levels for 24wks after therapy completed - Relapse: undetectable HCV RNA at end of therapy but detectable 24wks after completion - Viral breakthrough: HCV RNA level >1000 IU/ml after an undetectable level. - Incomplete Virologic Response (IVR): increase of 1 log_{10} IU/ml from nadir w/ HCV RNA	-Response rates were significantly higher among patients receiving boceprevir regimens than controls. - SVR for non-blacks was 40% in the control group compared to 67% in group 2 and 68% in group 3 ($p<0.001$). - SVR for blacks was 23% in control group compared to 42% in Group 2 ($p=0.04$) and 53% in group 3 ($p=0.004$). -At 4 weeks, 23% of non-blacks and 38% of blacks had a decrease of < 1 log_{10} which was associated with lower rates of SVR. -In group 2, 22% of patients had detectable HCV RNA levels between 8-24wks and received therapy for >28wks. Of patients with detectable HCV RNA at 8 weeks 74% in group 2 and 74% in group 3 had SVR. (24 wks vs 44wks boceprevir therapy). -Fatigue, headache and nausea were the most common ADE's and	- Compared to controls both blacks and non-blacks had significantly increased response with the addition of boceprevir to therapy. The response was seen in patients whose HCV RNA viral load decreased by less than 1 log_{10} IU/ml at 4wks. Patients with undetectable viral load at wk 8 had higher rates of SVR regardless of treatment regimen. Patients who had response guided therapy (group 2) had significantly higher SVR compared to controls.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
				level >1000 IU/ml	dysgeusia occurred twice as often in the boceprevir groups. - Anemia was reported in 29% of controls and 49% of boceprevir groups. - Grades 1, 2, 3, and 4 anemias in control groups were 36%, 17%, 2% and 0% compared to 43%, 31%, 3% and 1% in boceprevir groups. - 13% of controls and 21% of boceprevir patients required dose reduction due to anemia. Erythropoietin was administered in 24% of controls and 43% of boceprevir patients. - Significantly more patients in the boceprevir groups 24% (group 2) and 25% (group 3) had grade 3 neutropenia (ANC 500-750) vs control 14% (p<0.001).	**CHC Comments:** -Randomization was stratified by baseline HCV RNA levels and HCV genotype. Designed as a superiority study, primary outcome assessed as ITT, secondary outcomes M-ITT, black vs non-black cohort was per-protocol. Therapy was discontinued in all groups if levels remained detectable at 24wks
Bacon et al[48] 2011 **LOE: 1a**	Randomized double blind, placebo controlled multicenter	N=403	-Patients with responsiveness to interferon therapy at a minimum of 12weeks. (met either of	-Sustained Virologic Response (SVR) -Viral breakthrough: HCV RNA level >1000 IU/ml after an undetectable level	-Overall SVR rates were 21%, compared to 59% and 66% in groups 1, 2, and 3 respectively (p<0.001 for 1 vs 2 and 1 vs 3). -Response rates at end of treatment were 70% and 77% in	-Boceprevir added to standard therapy improves SVR in patients that have failed previous interferon therapy. Patients with

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	P: peginterferon alfa 2b 1.5mcg/kg QW **R**: Weight based RBV 600-1400mg/d **B**: boceprevir 800mg TID **Control:** PR x 4wks then PR + Placebo x 44wks Vs **Group 2:** PR x 4wks then PRB x 32wks - if HCV RNA undetectable at 8 and 12wks stop therapy - if HCV RNA detectable at 8wks and undetectable at 12wks THEN PR + Placebo x 12wks Vs **Group 3:** PR x 4wks then PBR x 44wks	72 weeks	the 2 criteria below) <u>Non-response:</u> decrease in HCV RNA by 2log by wk 12 but w/ detectable levels during therapy <u>Relapse:</u> undetectable HCV RNA at end of treatment but detectable HCV RNA during follow-up period.	and Incomplete Virologic Response (IVR): increase of 1 log_{10} IU/ml from nadir w/ HCV RNA level >1000 IU/ml were assessed	group 2 and 3 respectively compared to 31% in group 1. -Relapse rates were significantly lower in group 2 (15%) and group 3 (12%) compared to control (32%). -Viral breakthrough occurred in 1% of patients in group 1, 6% in group 2 and 4% in group 3. - In prior relapse patients, SVR rates were 29%, 69% and 75% in groups 1, 2 and 3 respectively. -In prior non-response patients, SVR rates were 7%, 40% and 50% in groups 1, 2 and 3 respectively. -In poor response to PR lead in, 15%, 28% and 27% of patients in groups 1, 2 and 3 respectively had poor response to PR lead in (<1log_{10} decrease in HCV RNA at 4wks). Of these patients, SVR was achieved in 0%, 33% and 34% of patients in groups 1, 2 and 3 respectively. -Patients with good response to	virologic response at 8 weeks had similar SVR rates when treated for 32 weeks compared to 44 wks of triple therapy. **CHC Comments:** Study funded and data analyzed by drug manufacturer.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					PR lead in therapy (>1log_{10} decrease in HCV RNA at 4wks) achieved SVR rates of 25%, 73% and 79% in groups 1, 2 and 3 respectively. <u>Response guided therapy:</u> -At week 8, the number of patients with undetectable HCV RNA levels was 9%, 46% and 52% in groups 1, 2 and 3 respectively. - There was no difference in SVR rates between groups 2 and 3 (OR 1.4, 95%CI: 0.9-2.2). -Factors significantly associated with achieving SVR: randomization to boceprevir group 2 or 3(OR 7.3, 10.7 respectively p<0.001), previous relapse (OR vs non-response 3.1, p<0.001), low viral load at baseline (OR vs high load 2.5, p=0.02), absence of cirrhosis (OR vs presence 2.1, p=0.04). - 61% of patients discontinued therapy at week 12 due to no response (detectable HCV RNA at 12wks) in group 1 compared to 22% and 18% in group 2 and 3.	

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					- Anemia occurred in 43-46% of boceprevir groups compared to 20% in control (p<0.001). - More patients discontinued therapy due to ADE in the boceprevir treated groups (8-12%) vs 2% (p=0.02).	
Mc Hutchinson et al[49] 2010 **LOE: 1b**	Randomized, partially placebo controlled, partially double blind, phase 2 study **P**: peginterferon alfa 2a 180mcg qwk **R**: ribavirin BID **T**: telaprevir 1125mg x1 then 750mg q8h **PR48:** PR + placebo x 24wks then PR x 24wks (Control) **T12PR24:** TPR x 12 wks then PR + placebo x 12 wks **T24PR48:** TPR x 24wks then PR x 24wks **T24P24** TP x 24wks	N=453 72 weeks	-Aged 18-70yrs with HCV genotype 1 previously treated with Peginterferon alfa and ribavirin with no SVR after at least 12 weeks. *Non-response:* undetectable levels never achieved during or at the end of therapy *Relapse:* undetectable HCV RNA for at least 42wks but detectable	- SVR: undetectable HCV RNA level 24 weeks after last study dose -Logistical regression variables included treatment assignment, race, previous virologic response, baseline HCV RNA level, HCV genotype, age. - Post Hoc variables added included: sex, BMI, presence of cirrhosis.	-SVR rates were significantly higher in telaprevir treated groups, T12PR24 (51%), T24PR48 (53%) and T24P24 (24%) compared to PR48 (14%) [p<0.001, p<0.001, p=0.02 respectively). -Response rates at the end of treatment period, at weeks 4 and at week 12 were all higher in the telaprevir groups. -Relapse rates were 30%, 13% and 53% in the T12PR24, T24PR48 and T24P24 groups compared to 53% in the PR48 group. -Virologic break through at week 24 was 13%, 12% and 32% in the T12PR24, T24PR48 and T24P24 groups compared to 3% in the PR48 group. In the telaprevir	- There was a higher breakthrough rate, relapse rate and lower SVR in the T24P24 treatment arm. Ribavirin therapy should be included with telaprevir and interferon therapy. Relapse patients were more likely to have SVR than non-responders when treated with telaprevir. **CHC Comments:** Randomization stratified to balance race and previous virologic

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			levels observed during follow up *Breakthrough:* Undetectable levels during treatment period but detectable levels before the end of treatment.		groups those with breakthrough were mostly non-responders. -In previous non-response, SVR rates were 39%, 38% and 11% in the T12PR24, T24PR48, and T24P24 groups compared to 9% in the PR48 group. -In those with previous relapse, SVR rates were 69%, 76% and 42% in the T12PR24, T24PR48 and T24P24 groups compared to 20% in the PR48 group. -SVR was significantly associated with T12PR24 and T24PR48 groups, an undetectable HCV RNA level during previous PR therapy, and low baseline viral load (<800,000 IU/ml) -Rash and pruritus were more common in the telaprevir groups than PR48 group. The incidence was 50% in T12PR24 and 60% in T24PR48 groups compared to 20% in PR48. -Severe grade 3 rash occurred in 5% of T12PR24, 4% of T245PR48	response

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					and 3% of T24P24 compared to 0% in PR48.	
Jacobsen et al[50] 2011 **LOE 1b**	Randomized, double blind, placebo controlled multicenter **P**: peginterferon alfa 2a 180mcg qwk **R**: Ribavirin >75kg: 600mg BID <75kg: 500mg BID **T**: Telapravir 750mg q8h **PR:** PR + placebo x 12wks then PR x 36wks **T12PR:** TPR x 12wks -undetectable at 4 & 12W then 12wks PR -detectable at 4 or 12wks then 36W PR **T8PR:** TPR x 8 wks then PR + placebo x 4wks -if undetectable at 4 & 12wks then 12wks PR	N=1088 72 weeks	-Aged 18- 70yrs old, treatment naïve patients with HCV genotype 1 infection with evidence of chronic hepatitis on liver biopsy w/in 1yr. ANC >1500/cm^3; Hgb >13 in males, >12mg/dl in females, Plts >90,000/cm^3	-Proportion of patients achieving SVR 24wks after last planned dose of study drug -Proportion of patients with undetectable HCV RNA at 72 weeks, 4 weeks, 12 weeks, both 4 and 12 weeks, end of treatment, 12 weeks after last study dose, -Relapse: undetectable levels at end of study but detectable during follow up	-The proportion of patients achieving SVR was significantly higher in the telaprevir groups (75%, T12PR and 69% T8PR) compared to 44% in the PR group (p<0.001 for both telaprevir groups vs PR). -Undetectable HCV RNA levels at 72wks were present in 73% and 67% of T12PR and T8PR groups compared to 44% in the PR group (p<0.001 for both comparisons). <u>Rapid Virologic response:</u> -Undetectable levels at 4 weeks were present in 68%, 55% and 9% of the 3 groups respectively. <u>Extended rapid virologic response:</u> -Undetectable levels at 4 and 12wks were present in 58%, 57% and 8% of the 3 groups respectively. -Of the extended rapid virologic response, patients assigned to 24 weeks of therapy, 89% and 83% in the T12PR and T8PR groups met	-Telaprevir increases the rate of SVR when added to patients treated with interferon and ribavirin. Early rapid virologic response was seen in more than half of patients treated with Telaprevir. Shorter therapy with PR in these patients did not result in increased relapse rates; however, telaprevir therapy was associated with a higher incidence of adverse effects compared to PR therapy. **CHC Comments:** Randomization stratified per HCV genotype and baseline viral load.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	- if detectable at 4 or 12wks then 36wks PR				criteria for SVR. <u>Black patients</u>: -62% and 58% in the T12PR and T8PR groups had SVR compared to 25% in the PR group. -Relapse occurred in 9% of the T12PR and T8PR groups compared to 28% in the PR group. -Rates of virologic failure were lower in the telaprevir groups 8-13% compared to 32% in the PR group. -Nausea, diarrhea, pruritus, rash and anemia were at least 10% greater in telaprevir treated patients than in the PR group. -10% of telaprevir patients discontinued the study due to ADE's compared to 7% in the PR group. -Anemia and rash were the 2 most common ADE's leading to discontinuation in the telaprevir groups. - 7% of T12PR and 5% of	Only 9% of the studied population was of Black ethnicity. Prespecified stopping rules (virologic failure): Telaprevir patients with HCV level >1000 at wk 4 would discontinue telaprevir but continue PR. Pts with <2log decrease at wk 12 discontinued therapy. Pts discontinued therapy if HCV RNA was detectable at any time between 24 and 40 weeks

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					T8PR patients discontinued due to rash - 1% of T12PR and 3% of T8PR patients discontinued due to anemia. - 17 patients in the T12PR and 17 patients in the T8PR group received blood transfusions compared to 6 in the PR group.	
Zeuzem et al[51] 2011 **LOE: 1a**	Randomized Multicenter **P**: peginterferon alfa 2a 180mcg qwk **R**: ribavirin >75kg: 600mg BID <75kg: 500mg BID **T**: telaprevir 750mg q8h	N=663 72 weeks	-Patients aged 18-70 yrs with chronic HCV genotype 1 infection with no SVR to a previous course of PR despite receiving 80% of the doses. ANC >1200/cm^3; Hgb >12mg/dl women, >13mg/dl men; Plts >90,000/cm^3	-Proportion of patient's w/ relapse or lack of previous response who had SVR (no HCV RNA 24wks after last dose) -Effect of lead-in treatment with PR on SVR, proportion of pts with undetectable HCV at 4 and 8 wks, proportion of patients with relapse, change from baseline	-The proportion of patients with SVR was significantly higher in the telaprevir groups compared to the control groups. - Overall SVR rates were 64% in T12PR48, 66% in Lead-in T12PR48 and 17% in control (p<0.001 for both telaprevir groups vs control). <u>Pt's w/ previous relapse:</u> -SVR: 83% 88%, and 24% in T12PR48, lead-in T1248 and control respectively (p<0.001) -Virologic failure: 1% telaprevir vs 26% control group.	- Addition of telaprevir to PR therapy significantly improved SVR rates in patients who previously received therapy. - Response rates were increased in all subgroups of patients who failed previous therapy including those with no response to previous therapy.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	T12PR48: TPR x 12wks then PR + placebo x 4wks then PR x 32wks Vs **Lead-in T12PR48:** PR + placebo x 4wks then TPR x 12 wks then PR x 32wks Vs **PR48 (control):** PR + placebo x 16wks then PR x 32wks			in log_{10} HCV RNA were also assessed *No response*: < 2 log_{10} decrease in HCV RNA after 12 weeks of therapy. *Partial response:* ≥2 log_{10} decrease in HCV RNA after 12 weeks of therapy but detectable HCV RNA levels. *Relapse:* undetectable HCV RNA at the end therapy with HCV RNA positivity thereafter.	<u>Pt's w/no previous virologic response or partial response:</u> -SVR: 41%, 41% and 9% respectively (p<0.001) <u>Pts with previous partial response</u>: -SVR: 59%, 54% and 15% respectively (p<0.001) -Virologic failure: 18%, 19% and 70% respectively. <u>Pts with previous no-response:</u> -SVR: 29%, 33% and 5% respectively (p<0.001) -Virologic failure: 57%, 47% and 84% respectively -Pooled subgroups of previous relapse or partial response treated with telaprevir had a higher SVR (78%) vs. 21% control (p<0.001). -Adverse events occurring in >25% of telaprevir groups included fatigue, pruritus, rash, nausea, influenza like illness, anemia and diarrhea.	This represents a group of patients that was no evaluated in the boceprevir trials. There was no significant difference between groups receiving lead in PR therapy and those that did not. Virologic failures were lower in patients with previous relapse or partial response. **CHC Comments:** -Randomization stratified by baseline viral load and previous response. All ITT analysis conducted

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					- Grade 3 ADE's occurred in 37% of telaprevir treated patients vs. 22% of controls. -Rate of grade 3 rash was 3% and a grade 3 pruritus was 1% in telaprevir groups compared to 0% in control. 4% of telaprevir patients discontinued therapy due to rash vs 0% in control. - Stopping rules (Virologic failure): Treatment was discontinued if HCV RNA levels were >100million at wks 4, 6, and 8 after telaprevir tx, if pts had <2$\log_{10}$ decrease in HCV RNA after 12 wks in T12PR48 group and the control group or at wk 16 in the lead-in T12PR48 group, or if HCV RNA was detectable at 24 or 36wks.	
Marcellin et al[58] 2011 **LOE 2**	Randomized prospective open label multicenter Phase 2 12wks of TEL (telaprevir) followed by PEG-INF/RBV for 12 or 36W per virologic response.	N=161	-Aged 18-65y, treatment naïve patients with chronic HCV genotype 1	-SVR -RVR, Virologic breakthrough- inc in HCV RNA levels >1$\log_{10}$ compared w/ nadir or value >100IU/ml if previously undetectable, and	-RVR was 80.0%, 69.0%, 82.5%, and 66.7% in Groups 1, 2, 3, and 4 respectively. - RVR in the pooled q8h group was similar to that in the pooled q12h group (74.4% vs 74.7%). - RVR rate in the pooled PEG-INF	-There was a high rate of SVR (81-85%) regardless of PEG-INF therapy or telaprevir dosing frequency. **CHC Comments:** Randomization was stratified per

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	Group 1: TEL 750mg q8h + PEG-INF 2a + RBV **Group 2:** TEL 750mg q8h + PEG-INF 2b + RBV **Group 3:** TEL 1125mg q12h + PEG-INF 2a + RBV **Group 4:** TEL 1125mg q12h + PEG-INF 2b + RBV PEG-INF 2a: 180mcg/wk with RBV at 1000-1200mg/d PEG-INF 2b: 1.5mcg/kg/wk with RBV			relapse- confirmed detectable HCV RNA during follow up when undetectable at EOT were also assessed	2a group was higher than in the pooled PEG-INF 2b group (81.3% vs 67.9%). -SVR was similar in all 4 treatment groups: 85.0%, 81.0%, 82.5%, and 82.1% of the patients from Groups 1, 2, 3, and 4 respectively - SVR rate was 82.9% in the pooled telaprevir q8h group, 82.3% in the pooled telaprevir q12h group. - SVR rate was 83.8% in the pooled PEG-INF 2a group and 81.5% in the pooled PEG-INF 2b group. -Relapse was observed in 9 patients: 3, 2, 3, and 1 in groups 1, 2, 3 and 4, respectively. -A total of 14 (8.7%) viral breakthroughs were observed in 1, 6, 3, and 4 patients in groups 1, 2, 3 and 4, respectively. -There were no significant adverse events or deaths during the study.	genotype and baseline viral load. - Pts w/undetectable viral loads wk 4-20 received a total of 24wks of tx. Otherwise the received 48wks

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Hayashi et al[67] 2012 **LOE-See CHC Comments**	Phase 3 controlled trial telaprevir 750mg q8h pc + Pegintron® 1.5mcg/kg/wk SQ + ribavirin (RBV) ≤60kg: 600mg/d >60-≤80kg: 800mg/d >80kg: 1000mg/d x12 Weeks: Then, Pegintron® + RBV x 12W	N= 168 48 weeks	-Relapsers: CHC treated patients with undetectable HCV RNA during INF or PEG tx Nonresponders: CHC treated patients who never had an undetectable HCV RNA for >24wks with INF or PEG	-SVR defined as undetectable HCV RNA at 24wks after end of therapy. -Relapse- undetectable serum HCV RNA at end of therapy and reappearance of HCV RNA during follow up. -Breakthrough- undetectable serum HCV RNA and reappearance during therapy -Nonresponse- state of continuously detectable serum HCV RNA during treatment -Adverse events	Efficacy in Relapsers: - SVR was 88.1%; nonresponse was 0.9%, breakthrough was 0.9% and relapse was 7.3%. - The rapid viral response rate was 87.2% and the end of treatment response rate was 94.5%. - Patients achieving undetectable HCV RNA at ≤4 weeks had significantly higher SVR (91.8%) vs those that achieved SVR after 4 weeks (66.7%), p=0.0487. - The SVR was significantly higher for men compared to women (93.9% vs79.1%, p=0.0316) Efficacy in non-responders: - SVR was 34.4%; nonresponse was 6.3%, breakthrough was 18.8% and relapse was 40.6%. - The rapid viral response rate was 71.9% and the end of treatment response rate was 59.4%. - There was no difference in SVR based on any subgroup analysis. -Serious adverse events were reported in 11.9% of patients in	-Telaprevir in combination with PEG-INF + RBV may be effective in achieving SVR for patients with relapsed or non-response to PEG-INF/RBV therapy. **CHC Comments:** This was a cohort study of patients with disease. The results were not compared to patients treated with placebo. There was no randomization described. Significant bias may occur.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					the relapser group and 9.4% in the non-responder group. -Study discontinuation due to adverse events occurred in 17.4% of relapsers and 12.5% in nonresponders. -There was one death due to PE that was classified as 'possibly' related to telaprevir -Skin disorders were reported in 82.3% of all patients, grade 3 disorders were reported in 6.4% and 6.3% of patients in the relapser and nonresponder groups respectively.	
Susser et al[68] 2011 **LOE 2**	Longitudinal Cohort from phase 1 (R, DB, PC) trials of boceprevir and telaprevir telaprevir alone: 450mg TID; 750mg TID; 1250mg TID telaprevir 750mg TID + PEG-INF alfa2a (180mcg/wk) x2wks	N= 28 median 4.2 yrs	-Patients with chronic HCV genotype 1 enrolled in phase 1b trials	-Clonal sequences for evidence of potential persistence of viral variants at 36, 54, 55, 155, 156, 170.	-Resistance analysis: -Telaprevir: only wild type NS3-protease variants were present in 12 of 14 patients. - 1 patient had V36M variant at 4% frequency which was present at the end of telaprevir therapy - 1 patient had V36A and A156T variant which confers the highest resistance to telaprevir -Boceprevir: 9 of 14 patients	-Treatment with direct dna agonist's boceprevir and telaprevir resulted in initial selection of highly resistant strains of HCV however these mutations disappeared shortly after withdrawal of therapy.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	boceprevir alone: 200mg BID; 400m BID; 400mg TID boceprevir 400mg TID or 400mg QID or 600mg QID + PEG-INF alfa 2b (1.5 mcg/kg/wk) x 2 wks				showed no resistant variants - 1 pt had 94% of closes with T54S+R155K and 3% with T54S variants at 3yrs. - 1 pt had T54A which decreased to undetectable at end of treatment and V55A which was 13% at end of treatment. V36M and V36M+R155K variants both present at EOT decreased to undetectable at 3.75yrs. - 1 patient had V55A at 95% and T54S+V55A at 5% after 4.75yrs. - 1 pt had V36A at baseline that decreased to undetectable after boceprevir monotherapy. - 1 pt had v5 present 5.25yrs after therapy.	**CHC Comments**: A limitation of this study is the small sample size.
Yang et al[79] 2013 **LOE 1b**	Systematic review, meta-analysis of randomized controlled trials (RCT)	N= 2,759	- Patients with chronic hepatitis C virus (HCV) genotype 1 infection	- Sustained virologic response (SVR) rate, defined as undetectable HCV RNA level 24 wks after the end of therapy	- SVR rate was significantly higher in the TPR group (1,284/1,932, 66.5%) than in the PR group (296,827, 35.8%) with a pooled OR [3.81, 95% CI 2.43-5.96, p<0.001]. - Relapse rate was significantly lower in the TPR group	- Telaprevir-based regimens were found to significantly increase the SVR rate and reduce the relapse rate in patients with HCV

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	telaprevir +PEG-INF + ribavirin (TPR) Vs PEG-INF + ribavirin (PR)	24- 48 weeks	- Median age ranging from 46-55	-Viral relapse, detectable HCV RNA level during the 24-wk post-treatment period in patient with undetectable HCV RNA levels at the end of treatment. - Serious adverse events, defined as grade 3 or 4 - Adverse events	(190/1,484, 12.8%) then in the PR group (140/425, 32.9%) with a pooled RR (0.40; 95% CI 0.24-0.66, p<0.001). -Increased risk of serious adverse events in the TPR group (RR=1.45, 95% CI 1.12-1.87, p=0.005).	genotype 1 infection. - However, telaprevir-based regimens may cause an increased risk of serious adverse events, and safety of this regimen requires further study. **CHC Comments:** Limitations: -The efficacy of telaprevir in patients with other genotypes (besides 1) requires further study. The efficacy of telaprevir over 12 weeks was studied, efficacy of telaprevir for over 24 weeks remain unclear
Chou et al[80] 2013 **LOE 1b**	Systematic review, meta-analysis of randomized trials and cohort studies	N = 61,619	- Adults with chronic HCV infection and antiviral-naïve	- Sustained virologic response (SVR), defined as the absence of	- Dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a lower SVR than was pegylated interferon	- SVR rates for genotype 1 infection are higher with triple therapy

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	Group A: pegylated interferon alfa-2b + ribavirin Vs pegylated interferon alfa-2a + ribavirin **Group B:** pegylated interferon (alfa-2b or-2a) + ribavirin + telaprevir or boceprevir Vs dual therapy	24-48 weeks		detectable HCV RNA in the serum 6 months after the end of therapy. - Mortality, cirrhosis, hepatic decompensation, hepatocellular carcinoma, and need for transplantation - Harms from antiviral therapies: influenza-like symptoms, hematologic effects, and psychiatric effects.	alfa-2a plus ribavirin, RR 0.87; 95% CI, 0.80-0.95 (absolute difference, 8% points [95% CI, 3-14% points]) based on 7 poor-to fair-quality trials. - Genotype 2 or 3 infection, dual therapy for 12-16 weeks was associated with lower SVR than for 24 weeks, and lower doses of pegylated interferon alfa-2b were less effective than standard doses. - For genotype 1 infection, fair-quality trials found that triple therapy was associated with higher SVR than dual therapy. - Compared with dual therapy, boceprevir triple therapy increased risk for hematologic adverse events and telaprevir increased risk for anemia and rash. -In the largest study (N=16, 864) that mostly included male VA population, SVR after antiviral therapy was associated with a lower risk for all-cause mortality vs no SVR, after a median of 3.8	that includes a protease inhibitor than with standard dual therapy. - An SVR after antiviral therapy appears associated with improved clinical outcomes. **CHC Comments:** Limitations included that the analyses for publication bias were not performed, due to the small numbers of trials; included were highly selected populations; observational studies did not always adequately control for confounders; and almost all trials were funded by pharmaceutical

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					years (adjusted HR 0.71). -Of the other 18 cohort studies, there was also a result that SVR was found to be associated with a decreased risk for all-cause mortality (aHR 0.07-0.39), liver-related mortality (aHR 0.04-0.27), and hepatocellular carcinoma (aHR 0.12-0.46) as compared with no SVR.	companies.
Sitole et al[81] 2013 **LOE 1b**	Meta-analysis, prospective Phase II and III randomized controlled trials telaprevir or boceprevir or placebo + PEG-interferon + ribavirin (peg-IFN + RBV)	N= 4,144 24-48 weeks	- Treatment-naïve and treatment-experienced patients with chronic hepatitis C virus (HCV) genotype 1 infection - Mean or median age, ~49 years (range, 18-70 years)	- Sustained virologic response (SVR), undetectable HCV RNA 6 months after last dose - Rapid viral response to treatment and the rate of rate of relapse - Adverse events as a result of discontinuation or use of either protease inhibitors	- With telaprevir, the ORs (95% CI) for SVR at 24 weeks in treatment-naïve and treatment-experienced patients were 3.31 (2.27-4.82; P < 0.0001) and 4.21 (1.83- 9.72; P= 0.001), respectively. - Telaprevir triple therapy did not result in more drug-related discontinuations, but did cause additional rash, pruritus, and anemia. - Boceprevir, the ORs (95% CI) were improved in both treatment groups (3.55 [2.66-4.56; P< 0.0001] and 7.34 [3.92- 13.9; P < 0.0001]), but with more treatment-related anemia and dysgeusia.	- Telaprevir or boceprevir combined with Peg-IFN + RBV had favorable short-term data on SVR, while resulting in more drug-related adverse events. -Extended follow-up is required to determine whether these agents offer reduction in the risk for chronic hepatitis C genotype 1-related mortality and/or hospitalization.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Cooper et al[82] 2013 **LOE 1b**	Meta-analysis, Phase II and III randomized controlled trials **Standard-duration therapy:** Peg-IFN α-2a + RIB (x48 wks) Vs Peg-INF α2b + RIB (x48 wks) And TVR + Peg-IFN α-2a or -2b + RIB Vs BOC + Peg-IFN α-2a or -2b + RIB **Response-guided therapy**: TVR + Peg-IFN α-2a or -2b + RIB Vs BOC + Peg-IFN α-2a or -2b + RIB	N= 5,851 48 weeks	- Treatment-naïve and treatment-experienced adults with genotype 1 hepatitis C virus (HCV) infection	- Sustained virologic response (SVR) - Rate of relapse, reoccurrence of HCV RNA within the 24-week post-therapy follow-up period - Discontinuation due to adverse events - Anemia, neutropenia, thrombocytopenia, rash, and pruritus	- Treatment naïve patients, clinical outcomes were similar for boceprevir and telaprevir, for SVR OR 0.90, 95% CI (0.41-1.91). Among treatment-experienced patients, SVR OR 1.45, 95% CI (0.70-3.08) - Relapse rate: among treatment naïve patients OR 1.09, 95% CI (0.19-4.84). Among treatment-experienced patients OR 0.35, 95% CI (0.13-1.02). - Treatment-naïve patients, telaprevir yielded lower rates of anemia and neutropenia, but higher rates of rash and pruritus. For treatment-experienced patients, all adverse event rates were higher with telaprevir.	- Boceprevir and telaprevir exhibit similar effects among hepatitis C genotype 1 treatment-naïve and treatment-experienced patients. TVR and BOC both yielded higher SVR rates, lower relapse rates, and higher discontinuation rates than the two PEG-INFα plus RIB regimens. **CHC Comments:** Limitations: -Small number of included studies - BOC trials did not include null responders, while TVR did - Erythropoietin was used to manage anemia in the BOC trial, not in the TVR trials

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Kieran et al[83] 2013 **LOE 1b**	Systematic review & meta-analyses telaprevir + PR Vs boceprevir + PR	N= 4,211 Duration not specified	- Treatment-naïve and treatment-experienced adults with genotype 1 hepatitis C virus (HCV) infection - Treatment-naïve group included a prespecified subgroup analysis of patients with black ethnicity	- Relative efficacy among the two treatments	- Prior treatment "relapsers": telaprevir had greater relative efficacy then boceprevir (OR, 2.61 [95% CI, 1.24-5.52]) -There was no statistical significance in relative efficacy for other categories. - Treatment-naïve patients: boceprevir vs. standard care (OR, 3.06 [95% CI, 2.43-3.87]); telaprevir vs. standard care (OR, 3.24 [95% CI, 2.56-4.10]); telaprevir vs. boceprevir (OR, 1.06 [95% CI, 0.75-1.47]). Patients with black ethnicity had increased efficacy with either triple therapy; (boceprevir + PR: OR, 3.58 [95% CI, 1.84- 7.31]; telaprevir + PR: OR, 5.99 [95% CI, 2.17- 17.87]) - Total treatment-experienced population: boceprevir vs. standard of care (OR, 6.53 [95% CI, 4.20-10.32]); telaprevir vs. standard of care (OR, 8.32 [5.69-12.36]); telaprevir vs. boceprevir (OR, 1.27 [95% CI, 0.71-2.30]).	-Telaprevir had greater relative efficacy than boceprevir in patients who had previously relapsed, but there was insufficient evidence to detect a difference in treatment outcomes between the 2 agents in the overall population. Nevertheless, the overall magnitude of the treatment effect was greater in the treatment-naïve black subgroup.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Cure et al[84] 2012 **LOE 1b**	Systematic review, of randomized controlled trials PR (alfa-2a or 2b) + boceprevir or telaprevir	N = 6,708 48 weeks	- Treatment-naïve and treatment-experienced adults with genotype 1 hepatitis C virus (HCV) infection	- Sustained virologic response (SVR), undetectable HCV RNA level 24 weeks after the end of therapy - Efficacy of PR-based treatment in genotype 1 chronic HCV patients.	- Treatment-naïve patients: OR (posterior median [95% CI]) for telaprevir and boceprevir versus PR were respectively 3.80 (2.78-5.22) and 2.99 (2.23- 4.01). The OR for telaprevir versus boceprevir was 1.42 (0.89- 2.25), with probability for telaprevir being more effective (P[OR >1]) of 0.93 - Treatment-experienced patients: OR of telaprevir and boceprevir versus PR were respectively 13.11 (7.30- 24.43) and 5.36 (2.90-10.30). The OR for telaprevir versus boceprevir was 2.45 (1.02-5.80), with telaprevir having a probability of 0.98 of being more effective.	- In the absence of direct comparative head-to-head studies, an indirect comparison suggests better efficacy for telaprevir than boceprevir in both treatment-naïve and treatment-experienced patients **CHC Comments:** Limitations include the low number of trials, and that it did not consider safety between BOC and TVR.
Flamm et al[92] 2013 **LOE 1b**	Double-blind, placebo-controlled, multi-center	N = 201	Adults with HCV genotype 1 who have relapsed or have not responded to previous therapy.	-Sustained virologic response, undetectable plasma HCV RNA at follow-up week 24 -Adverse events	- The boceprevir group significantly increased the rate of SVR from 21% in the PEG2a/R group to 64% in the BOC/PEG2a/R group (p<0.0001). - Among patients with poor response to interferon therapy, 39% in the BOC/PEG2a/R group had SVRs, compared to none in	- The addition of boceprevir after 4 weeks of lead-in therapy with PEG2a/R caused significantly higher rates of SVR in previously treated patients with chronic HCV

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	PEG-IFN α-2a (180µg/wkly) + RBV (1000- 1200 mg/d) + placebo Vs PEG-IFN α-2a (180µg/wkly) + RBV (1000- 1200 mg/d) + boceprevir (800mg 3x/day)	44 weeks			the other group. - Among patients with good response to interferon, 71% in the BOC/PEG2a/R had SVRs, compared to 25% in the other. - 50% of patients in the BOC/PEG2a/R group developed anemia, compared to 27% in the other group; 43% vs. 21%, respectively developed neutropenia.	genotype-1 infection, compared with patients given only PEG2a/R.
Buti et al[103] 2014 **LOE-2**	Randomized, open-label, multicenter trial telaprevir (TVR) 1125 mg BID, PEG-IFN α-2a 180 mcg/wk & RIB 1000-1200 mg/day x12W Vs TVR 750 mg TID, PEG-IFN α-2a 180mcg/ wk & RIB 1000-1200 mg/day x12W	N = 740 Follow-up: 24 weeks after the end-of-treatment	Adults with chronic HCV genotype 1 who were treatment naïve	- The proportion of patients in each treatment group who achieved a sustained virologic response at 12 weeks after end-of-treatment (SVR12) - Secondary efficacy variables included the proportion of patients who achieved rapid virologic response (RVR), achieved SVR at week 24, experienced a	- SVR12 was 74.3% with TVR twice daily and 72.8% with TVR every 8 hours. The adjusted difference in response between groups was 1.5% (95% CI, –4.9% to 12.0%), with the lower 95% CI (–4.9%) exceeding the non-inferiority margin of –11%. Thus, non-inferiority of TVR twice daily compared with every 8 hours was established. - The secondary end point, SVR at week 24, was achieved in 74.8% of patients treated with TVR twice daily and 72.8% of patients treated with TVR every 8 hours.	-Both TVR 1125 mg twice daily and 750 mg every 8 hours were shown to have high rates of SVR12, a low incidence of virological failure, and a comparable safety and tolerability profile when administered in combination with PEG-IFN/RBV.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	Both followed by PEG-IFN α-2a 180mcg/W & RIB 1-1.2g/ day x12W if level of HCV RNA at 4W <25 IU/ml or for 36W if ↑			relapse, and experienced on-treatment virological failure.	Relapse rates were similar between those treated with TVR twice daily (7.7%) and every 8 hours (6.5%). - On-treatment virological failure was observed in 38 (10.3%) and 36 (9.7%) patients treated with TVR twice daily and every 8 hours, respectively. -During the TVR treatment phase, those treated with TVR twice daily had a similar safety profile to that of those treated every 8 hours. Fatigue, pruritus, anemia, nausea, rash, and headache were the most frequent AEs, occurring in >25.0% of patients in both groups during the TVR.	
Fried et al[104] 2013 **LOE-1b**	Randomized, double-blind, multicenter	N=386	-Adults with chronic HCV genotype 1 who are treatment naïve	-The proportion of patients with undetectable HCV RNA (sustained viral resistance) at week 72 (SVR W72). -Secondary outcomes included SVR at 12 and 24 weeks after planned treatment	- The primary outcome measure, SVR W72, ranged between 70.7% and 84.8% for SMV regimens, compared with 64.9% of those treated with Peg-IFN and RBV alone. The differences between SMV 150-mg groups and control were statistically significant ($p<0.05$). - SVR24 was achieved in 74.7%-	-Simeprevir combined with peginterferon and ribavirin significantly improved sustained viral response rates (ranging between 75% and 86% between treatment arms) compared

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	simeprevir (SMV) 75 mg/ d x 12W, PEG-IFN α-2a 180 mcg/wk & RIB 1-1.2g/day x 24-48 weeks Vs SMV 150mg/d x 12W, PEG-IFN α-2a 180 mcg/wk & RIB 1-1.2g /day x 24-48W Vs SMV 75 mg/d x 24W & PEG- 2a 180mcg/ wk & RIB 1-1.2g/day x 24-48 weeks Vs SMV 150 mg/d x 24W, PEG-IFN α-2a 180 mcg/wk & RIB 1-1.2g/day x 24-48 weeks Vs PEG-IFN α-2a 180 mcg/wk & RIB 1-1.2g/day x 24-48 weeks	Follow up: 72 weeks		(SVR12 and SVR24). The incidence of adverse events (AEs) was monitored.	86.1% of those treated with SMV regimens, compared to 64.9% of those treated with placebo. All SVR24 comparisons between SMV treatment groups and placebo controls were statistically significant ($p<0.05$ or 0.005), except for SMV 75 mg for 24 weeks. - The most frequent AEs (fatigue, influenza-like illness, pruritus, headache, and nausea) were those typically associated with Peg-IFN and RBV therapy and were similar across SMV and placebo treatment groups. -Anemia was reported as an AE in 19.0%-22.1% of patients treated with SMV (all grade 1-2) and in 20.8% of those receiving placebo, and did not lead to discontinuation of SMV or placebo	with peginterferon and ribavirin alone, while having no substantial differences across simeprevir treatment regimens in the safety analyses.
Hayashi et al[105] 2014 **LOE-2**	Randomized, open-label, multicenter	N=92	-Adults with chronic HCV genotype 1b who were treatment naïve	-The proportion of patients with undetectable plasma HCV RNA 24 weeks after the end of treatment (SVR24).	-The SVR24 rate was higher in the simeprevir groups than in the PR48 group, with rates of 78%, 77%, 77%, 92% and 46% in the SMV12/PR24 50 mg, SMV24/PR24 50 mg, SMV12/PR24 100 mg, SMV24/PR24 100 mg and PR48	-In treatment naïve patients infected with HCV genotype 1b, treatment with simeprevir in combination with PEGIFN α-2a and

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	(SMV12/PR 24 50 mg): simeprevir 50 mg/d x 12W & PEG α-2a 180 mcg/wk & RIB 0.6-1g/day x 24W Vs (SMV24/PR 24 50 mg): simeprevir 50 mg/d x 24W & PEG-IFN α-2a 180 mcg/wk & RIB 0.6-1g/d x 24W Vs (SMV12/PR 24 100 mg): simeprevir 100mg/d x12W, PEG-IFN α-2a 180 mcg/wk, & RIB 600-1000 mg/day x 24W Vs (SMV24/PR 24 100mg): simeprevir 100mg/d x24W, PEG-IFN α-2a 180 mcg/wk, & RIB 600-1000 mg/day x 24W Vs (PR48): PEG-IFN α-2a 180 mcg/wk & RIB 1000-1200 mg/day x 48W	Follow-up: 24 weeks post-treatment		-Safety endpoints included the frequency and severity of adverse effects (AEs).	groups, respectively. -There were no clinically relevant differences in the incidence of AEs across the groups and the majority of AEs were of grade 1 or 2 in severity according to the WHO toxicity grading pre-defined in the study protocol. Rash and arthralgia, which were slightly higher ([15 % numerical difference) in the simeprevir groups than in the PR48 group, were also grade 1 or 2 in severity. -Incidences of anemia and decreased hemoglobin were similar in the simeprevir groups and the PR48 group.	ribavirin, regardless of simeprevir dose regimen (50 or 100 mg QD, for 12 or 24 weeks), demonstrated potent antiviral activity and high SVR rates vs PEG/ribavirin. Simeprevir was generally safe and well tolerated.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Sulkowski et al[113] 2013 **LOE-1b**	Randomized, double-blind, multicenter trial PEG-IFN α-2b 1.5mcg/kg/W & weight-based RIB (600-1400 mg/d) x4w followed by: PEG-IFN α-2b 1.5mcg/kg/W & RIB (600-1400 mg/d) x44W Or PEG-IFN α-2b 1.5mcg/kg/W & RIB (600-1400 mg/d) & boceprevir 800mg TID x44W	N=98 24 weeks of follow up at the end of 48 weeks of treatment	- Adults (18-65 years) with untreated HCV genotype 1 infection and controlled HIV (HIV RNA<50 copies/ml)	-The sustained virologic response (undetectable HCV RNA) at 24 weeks after the end of treatment. -Adverse events including HIV virologic breakthrough were monitored throughout the study.	-The primary outcome was achieved by 40 (63%) of 64 patients in the boceprevir group at follow-up week 24, compared with ten (29%) of 34 control patients (difference 33.1%, 95% CI 13.7–52.5, p=0.0008). - Adverse events were more common in patients who received boceprevir than in control patients: 26 (41%) versus nine (26%) had anemia, 23 (36%) versus seven (21%) pyrexia, 22 (34%) versus six (18%) decreased appetite, 18 (28%) versus five (15%) dysgeusia, 18 (28%) versus five (15%) vomiting and 12 (19%) versus two (6%) neutropenia. Three patients who received boceprevir plus peginterferon–ribavirin and four controls had HIV virological breakthrough. - HIV control was well maintained in patients taking boceprevir and HIV protease inhibitors. Drug interactions between boceprevir and HIV protease inhibitors did not have a clinically significant	-Boceprevir with peginterferon–ribavirin significantly increased the rate of sustained virologic response at follow-up week 24 compared with peginterferon–ribavirin alone in patients with HIV and previously untreated HCV genotype 1 infection.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					effect on HCV response or HIV control in this study.	
Pungpapong et al[114] 2013 **LOE-2**	Multicenter, retrospective chart review PEG-IFN α-2a 135 mcg/wk, RIB renal-dosed from 200mg 3x/wk to 800mg/day, &telaprevir 750mg Q8h x 12W then PEG-IFN α-2a 135 mcg/wk, RIB 200mg 3x/wk to 800 mg/day x 36W Or PEG-IFN α-2a 135 mcg/wk, RIB 200mg 3x/wk to 800 mg/day x 4W then PEG-IFN α-2a 135 mcg/wk, RIB 200mg 3x/wk to 800 mg/day & boceprevir 800mg Q8h x 44W	N=60 Follow-up: 12 to 66 weeks	-Adults with history of liver transplant and chronic HCV genotype 1	-Virologic response (undetectable HCV RNA) at 24 weeks of treatment. -Adverse effects including hematologic side effects were monitored.	-Per an intention-to-treat analysis, 14 of 21 TVR-treated patients (67%) and 10 of 22 patients who received BOC (45%) achieved undetectable HCV RNA levels at week 24 without viral breakthrough at the last follow-up. -Cytopenias were very common, and all patients required dose reductions of PEG-IFN and/or RBV of the administration of hematological growth factors. -Mild transient increases in serum creatinine from the baseline were noted in almost all patients during the first 12 weeks of TVR administration (range = 0-1.4 mg/dL, mean = 0.6 mg/dL). Serum creatinine increased from the baseline throughout the 44 weeks of BOC administration (range 0.1-1.0 mg/dL, mean 0.5 mg/dL). -One death occurred in each group.	-On treatment, virologic response rates of approximately 50% to 60% were achieved in this population, but numerous side effects (especially cytopenias) as well as 2 deaths highlight the potential hazards of these regimens in patients with liver transplant and chronic HCV.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Zeuzem et al[119] 2014 **LOE-1b**	Randomized, double-blind, multicenter trial simeprevir 100mg QD for 12 weeks Vs simeprevir 150mg QD for 12 weeks Vs simeprevir 100mg QD for 24 weeks Vs simeprevir 150mg QD for 24 weeks Vs simeprevir 100mg QD for 48 weeks Vs simeprevir 150mg QD for 48 weeks Vs placebo All groups including placebo also received PEG-IFN α-2b 180 mcg/wk and ribavirin 1000-1200 mg/day x 48 weeks	N = 462 Follow-up: 24 weeks after end-of-treatment	-Adults with chronic HCV genotype 1 who did not respond, had a partial response, or relapsed after treatment with peginterferon and ribavirin.	-The proportion of patients with sustained virologic response (SVR; undetectable HCV RNA) at 24 weeks after end-of-treatment. - Secondary efficacy end points included the proportion of patients with rapid virologic response (RVR; HCV RNA undetectable at week 4) and proportion of patients with SVR 12 weeks after the planned end-of-treatment. -Adverse events (AEs) were monitored throughout the study.	- In the overall population, SVR24 was achieved in 60.6%-80.0% of simeprevir arms and 22.7% of the placebo arm (p<0.001). -When pooling dosages, SVR24 was achieved by 129 of 197 patients (65.5%; range, 60.6%-69.7%) of the simeprevir 100-mg group and 145 of 199 patients (72.9%; range, 66.7%-80.0%) of the simeprevir 150-mg group, compared with 15 of 66 patients (22.7%) on placebo (p<0.001 for both comparisons). -Pooling treatment dosage durations, SVR24 was achieved by 90 of 132 patients (68.2%; range, 66.7%-69.7%) on simeprevir for 12 weeks, 92 of 133 (69.2%; range, 66.2%-72.1%) of those on simeprevir for 24 weeks, and in 92 of 131 (70.2%; range, 60.6%-80.0%) of those on simeprevir for 48 weeks. - The proportions of patients achieving SVR at 12 weeks (60.6%-80.0% of simeprevir- and 23% of placebo-treated patients) were	-Simeprevir (100 mg or 150 mg once daily) in combination with PegIFN/RBV was effective and well tolerated in this study of patients who had previously failed to respond to PegIFN/RBV treatment. Treatment with simeprevir and PegIFN/RBV resulted in significantly higher SVR rates compared with placebo. There was a trend for better efficacy with simeprevir 150 mg compared with simeprevir 100 mg.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					very similar to the proportions achieving SVR24. - Overall, the safety profile observed with simeprevir-based treatment was similar to that observed within the placebo arm in the current study and historically with PegIFN/RBV. -The incidence of AEs, the majority of which were grade 1 or 2 in severity, was comparable across all treatment groups. The most frequently reported AEs (>25% of patients) with simeprevir plus PegIFN/RBV were fatigue, headache, pruritus, influenza-like illness, and neutropenia. -No major difference was reported with respect to the incidence of serious AEs, occurring in 7.8% (n = 31) and 6.1% (n = 4) with simeprevir and placebo, respectively.	
Ioannou et al[121] 2013 **LOE - 2**	Multicenter, retrospective chart review	N = 3,696 BOC; N=759 TLV	-Adults with chronic HCV genotype 1 who were treated with triple drug	-The SVR, defined as a negative HCV RNA in all follow-up HCV RNA tests after the treatment end date,	-The vast majority of patients received PEG-IFN alpha-2a starting at full doses (180 mg/week). Only a minority of boceprevir-treated (9%) or telaprevir treated (3%)	-In this nationwide, real-world study of HCV genotype 1 infected patients who received

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	PEG-IFN α, ribavirin, and boceprevir (BOC) 800mg Q8h Vs PEG-IFN α, ribavirin, and telaprevir (TLV) 750 mg Q8h	Follow-up: up to 12 weeks after the end of treatment.	therapy from June 2011 to February 2013. Patients who received both boceprevir and telaprevir, had HIV, or had prior liver transplantation were excluded.	including at least 1 test > 12 weeks after the end of treatment.	patients received PEG-IFN alpha-2b. Approximately 10% of patients started at a lower than recommended dose of ribavirin. Boceprevir and telaprevir were prescribed at standard doses in all patients (800 mg every 8 hours and 750 mg every 8 hours, respectively). - The SVR rate was 52.2% for boceprevir and 47.3% for telaprevir among all patients, with great variability among clinically relevant subgroups. The highest SVR rates were observed among prior relapsers (63% for boceprevir, 70% for telaprevir) and the lowest SVR rates among prior null responders (30.2% for boceprevir, 28.6% for telaprevir). -There was no statistically significant difference between boceprevir and telaprevir with respect to SVR in univariate or multivariate analyses in the entire population or among cirrhotic, non-cirrhotic, treatment-naive, and treatment-experienced patients.	boceprevir-based or telaprevir-based antiviral therapy, the SVR rate was 51.5% overall, 42.7% among cirrhotic patients, 56.8% among treatment-naive patients, 64.2% among prior relapsers, 31.7% among prior partial responders, and 29.8% among prior null responders. Statistically significant differences in SVR rates between boceprevir and telaprevir after adjusting for potential confounders was not observed.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Benito et al[122] 2013 **LOE - 2**	Multicenter, retrospective chart review PEG-IFN α-2a, ribavirin, and boceprevir (BOC) Vs PEG-IFN α-2a, ribavirin, and telaprevir (TLV)	N = 33 treated with boceprevir and 73 treated with telaprevir	-Adults with chronic HCV genotype 1 with or without HIV co-infection.	-The rapid virologic response (RVR) defined as undetectable HCV RNA at week 4 for TLV and at week 8 for BOC.	-Overall, there were no significant differences between patients on BOC and TLV, except for the proportion with HIV coinfection (44% TLV and 24% BOC). -The rate of RVR was significantly higher on TLV than BOC (82% versus 59%; p=0.001). Besides treatment, RVR was significantly influenced by HCV subtype (83% for 1b versus 61% for 1a; p=0.04) and prior interferon exposure (89% in treatment-naïve versus 69% in treatment experienced patients; p=0.03). -In a multivariate regression analysis including treatment, baseline HCV RNA, HCV-1 subtype, prior interferon exposure, and HIV coinfection, only TLV use (OR 3.54 [95% CI 1.23-10.24]; P=0.02) and HCV subtype 1b (OR 3.26 [95% CI 1.17-9.09]; P=0.02) remained significantly associated with the achievement of RVR.	-Triple combination therapy with TLV produced higher RVR rates than with BOC in chronic hepatitis C patients. However, the design of this trial was retrospective and further research is needed to validate these results.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Osinusi et al[102] 2013 LOE-2	Randomized, open-label, single-center trial sofosbuvir 400 mg/d and ribavirin 1000-1200 mg/d x24 weeks Vs sofosbuvir 400 mg/d and ribavirin 600 mg/d x24 weeks	N = 50 Follow-up: 24 weeks after the end-of-treatment	-Adults with chronic HCV genotype 1 who are treatment naïve	- The proportion of participants with undetectable HCV viral load 24 weeks after treatment completion (sustained virologic response – SVR 24) - Safety endpoints included frequency and severity of adverse events, discontinuations due to adverse events, and safety laboratory changes.	-The SVR24 rates were 68% (95% CI, 46%-85%) in the weight-based group and 48% (95% CI, 28%-69%; p=0.20) in the low-dose group. - Twenty-four (96%) in each group achieved viral suppression by week 4. -The most frequent adverse events were headache, anemia, fatigue, and nausea, the severity of which ranged from mild to moderate. -The weight-based group experienced a higher incidence of hemoglobin decline, which was maintained through week 12, than did participants in the low-dose group (week 4, 37% vs 4%; p=0.005; week 12, 39% vs 4%; p=0.01).	-Treatment with a 24-week regimen of sofosbuvir and ribavirin resulted in an SVR rate of 68% in the weight-based ribavirin regimen vs 48% in the low-dose ribavirin regimen among patients with chronic HCV.
Jacobson et al[106] 2013 LOE-1b	Randomized, multicenter, double-blind trial	N = 278	-Patients with chronic HCV genotype 2 or 3 whom treatment with peginterferon was not an	-The rate of sustained virologic response (undetectable HCV RNA) at 12 weeks after end of treatment.	-The rate of sustained virologic response at 12 weeks after treatment was 78% (95% confidence interval [CI], 72 to 83) among patients receiving sofosbuvir and ribavirin, as compared with 0% among those	-In patients with HCV genotype 2 or 3 infection for which treatment with peginterferon was not an option, 12 weeks of

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	sofosbuvir 400 mg QD, RIB 1000 to 1200 mg/d per weight X12W Vs placebo	Follow-up: 12 weeks post-treatment	option. The most common reasons that interferon treatment was not an option were clinically significant psychiatric disorders (in 57% of patients) and autoimmune disorders (in 19%).	-Secondary outcomes were the rate of response by genotype and the rate of adverse events.	receiving placebo (p<0.001). -Among patients who received sofosbuvir and ribavirin, 93% of patients with HCV genotype 2 infections had a sustained virologic response, as compared with 61% of those with HCV genotype 3 infection. -Four patients who received sofosbuvir and ribavirin (2%) discontinued treatment, as compared with three who received placebo (4%). -The rates of serious adverse events were 5% in the group that received sofosbuvir and ribavirin and 3% in the placebo group.	treatment with sofosbuvir and ribavirin was effective. Efficacy was increased among patients with HCV genotype 2 infection.
Jacobson et al[106] 2013 **LOE-1b**	Randomized, multicenter, double-blind trial	N=201	-Patients with chronic HCV genotype 2 or 3 who had not had a response to prior treatment with an interferon containing regimen.	-The rate of sustained virologic response (undetectable HCV RNA) at 12 weeks after end of treatment compared to a historical control rate. -The secondary	-The rates of sustained virologic response achieved with sofosbuvir and ribavirin were superior to the historical control rate of 25%, with rates of 50% (95% CI, 40 to 60) in the 12-week group and 73% (95% CI, 63 to 81) in the 16-week group (p<0.001 for each comparison). -The secondary analysis comparing rates of sustained	-Compared to 12 weeks of therapy with sofosbuvir and ribavirin, for patients with genotype 3 infection who have not had a response to prior treatment with interferon, extending the

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	sofosbuvir 400 mg QD & RIB 1000-1200 mg/d x12W then 4W of placebo Vs sofosbuvir 400 mg QD & RIB 1000-1200 mg/d dosed by weight x16W	Follow-up: 12 weeks post-treatment		outcomes were the rate of response between the treatment groups, rate of response by genotype, and adverse event rates.	virologic response between the groups showed that patients receiving 16 weeks of treatment had a significantly higher rate of sustained virologic response than patients receiving 12 weeks of treatment (difference, -23% points; 95% CI, -35 to -11; p<0.001). -The rates of sustained virologic response among patients with HCV genotype 2 infection who received 12 weeks of treatment and those who received 16 weeks of treatment were 86% and 94%, respectively (difference, −8 percentage points; 95% CI, −24 to 9), as compared with 30% and 62% for 12 and 16 weeks of treatment, respectively, among patients with HCV genotype 3 infection (difference, -32% points; 95% CI, -48 to -15). -The rates of serious adverse events were 5% in the 12-week and 3% in the 16-week group.	duration of treatment to 16 weeks may provide an additional benefit.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Kowdley et al[107] 2013 **LOE-2**	Randomized, open-label, multicenter trial Genotype 1: sofosbuvir 400 mg QD, PEG-α-2b 180mcg/ wk, & RIB 1-1.2g/day x12w Vs sofosbuvir 400 mg QD, PEG-IFN α-2b 180 mcg/wk & RIB 1000-1200 mg/day x 24W Vs sofosbuvir 400 mg QD, PEG-IFN α-2b 180 mcg/wk, & RIB 1000-1200 mg/day x 12W then 12W of sofosbuvir Genotypes 4,5, or 6: sofosbuvir 400 mg QD, PEG-IFN α-2b 180 mcg/wk and ribavirin 1000-1200 mg/day x 24 weeks	N = 316 patients with genotype 1, 11 patients with genotype 4, and 5 patients with genotype 6 Follow up: 24 weeks post-treatment	-Adults with chronic HCV genotypes 1, 4, 5, or 6 who were treatment naïve	-The sustained virologic response (undetectable HCV RNA) at post-treatment week 24 by intention-to-treat analysis. -The rate of sustained virologic response at 12 weeks after end of treatment (SVR12) was a secondary outcome. Safety was assessed by review of adverse events.	-In patients with HCV genotype-1, SVR24 was achieved by 46 patients (89%, 95% CI 77–96) in cohort A, 97 patients (89%, 82–94) in cohort B, and by 135 (87%, 81–92) in cohort C. We detected no difference in the proportion of patients achieving SVR24 in cohort A compared with cohort B (p=0.94), or in cohort C (p=0.78). -Of the 11 patients with genotype 4 HCV, nine (82%, 95% CI 48–98%) achieved both SVR12 and SVR24. We recorded no virological failure in these 11 patients-the other two patients were lost to follow-up at the end of treatment. All five of the patients with genotype 6 HCV achieved SVR12 and SVR24 (100%, 48-100%). - Most patients (97-99%) had at least one adverse event during the study. The most common adverse events were those consistent with the known safety profile for peginterferon and ribavirin: fatigue, headache, and nausea. Most of these adverse events rated by treating clinician as mild	-High rates of SVR12 and SVR24 were observed among patients with genotype 1 in all three treatment groups, suggesting no additional benefit of treatment durations of longer than 12 weeks. Sofosbuvir was well tolerated and there appeared to be no additional benefit of extending treatment beyond 12 weeks.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					in severity. -The proportion of patients with genotype-1 who discontinued any study drug because of an adverse event was greater in the 24 week treatment cohort than in either of the other two 12 week cohorts (18% *vs* 5–6%; three [6%] of 52 patients in cohort A, 19 [18%] of 106 patients in cohort B, and seven [5%] of 155 patients in cohort C). -The most common adverse events that led to the discontinuation of any study drug were anemia and neutropenia, and these are associated with peginterferon and ribavirin treatment.	
Lawitz et al[108] 2013 **LOE-2**	Randomized, open-label trial	N= 122 with genotype 1 and 25 with genotype 2 or 3	-Treatment naïve adults with genotype 1, 2 and 3 HCV infection.	-Safety and tolerability. -Secondary outcome were intention-to-treat analysis of sustained virologic response (undetectable HCV RNA) at post-	All 3 groups with genotype 1 continued PEG-IFN & RIB 12-36W more. - The most common adverse events during sofosbuvir dosing (up to week 12) were fatigue, headache, nausea, chills, pain, insomnia, and rash. Most adverse events were mild or moderate in	-These data suggest further testing of the 400 mg once daily dose of sofosbuvir in interferon-containing and interferon-free regimens for a total duration of 12

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	Genotype 1: sofosbuvir 200 mg/d, PEG-IFN α-2b 180 mcg/ wk & RIB 1000-1200 mg/day x 12W Vs sofosbuvir 400 mg/d, PEG-IFN α-2b 180 mcg/ wk & RIB 1000-1200 mg/day x 12W Vs placebo, PEG-IFN α-2b 180 mcg/wk & RIB 1000-1200 mg/day x 12W Genotypes 2,3 sofosbuvir 400 mg/d, PEG-IFN α-2b 180 mcg/ wk & RIB 1-1.2g/day x 12W	Follow-up: 24 weeks post-treatment		treatment weeks 12 (SVR12) and 24 (SVR24).	severity. -Adverse events seen in the sofosbuvir groups were generally consistent with events seen during treatment with peginterferon and ribavirin. Fatigue, rash, fever, and diarrhea were more common in both sofosbuvir groups than in the placebo group. -Three patients (one in the sofosbuvir 200 mg group and two in the sofosbuvir 400 mg group) had grade 3 or greater increases in aspartate aminotransferase concentrations, with associated increases in alanine aminotransferase concentrations to grade 2 within 4 weeks of beginning study treatment. -Among the patients with genotype 1, compared with the placebo group, SVR12 and SVR24 were more common in the 200 mg sofosbuvir group (differences of 30%, 95% CI 12–49, p=0.001, and 28%, 9–46, p=0.0017, respectively) and in the 400mg sofosbuvir group	weeks across HCV genotypes, and that these regimens should be tested in a broader population of patients, including those with cirrhosis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					(differences of 32%, 13–51; p=0.0005, and 30%, 11–49, p=0.0006, respectively). -Of the 25 patients with genotype 2 or 3, 24 achieved both SVR12 and SVR24. The one patient who did not achieve SVR was lost to follow-up after the baseline visit.	
Lawitz et al[109] 2013 **LOE-2**	Single group, open-label study sofosbuvir 400 mg/d and PEG-IFN α-2b 180 mcg/wk and ribavirin 1000-1200 mg/day x 12 weeks	N=327 Follow-up: 12 weeks post-treatment	-Treatment-naïve adults with HCV genotypes 1,4,5 or 6	-The sustained virologic response 12 weeks after the end of therapy. -Treatment discontinuation due to adverse events.	-A total of 295 of the 327 patients (90%; 95% CI, 87-93) with HCV genotype 1, 4, 5 and 6; 98% had genotype 1 or 4. Rates of sustained virologic response did not differ greatly according to the HCV genotype: 89% for patients with HCV genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with HCV genotype 4. -Treatment discontinuation was uncommon (2%) among patients receiving 12 weeks of triple-drug therapy with sofosbuvir. -The most common adverse effects were fatigue (59%), headache (36%), nausea (34%), and insomnia (25%). Influenza-like symptoms (a common side	-In this single-group study of sofosbuvir combined with PEG-IFN-ribavirin, patients with predominantly genotype 1 or 4 HCV infection had a rate of sustained virologic response of 90% at 12 weeks. High rates of sustained virologic response were observed among patients with genotypes 1a and 1b infection.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					effect of interferon therapy) were reported by 16% of patients.	
Lawitz et al[109] 2013 **LOE-2**	Randomized, open-label, controlled trial sofosbuvir 400 mg/d and ribavirin 1000-1200 mg/day x 12 weeks Vs PEG-IFN α-2b 180 mcg/wk and ribavirin 1000-1200 mg/day x 24W	N=499 Follow-up: 12 weeks post-treatment	Treatment-naïve adults with HCV genotypes 2 or 3	-The sustained virologic response (SVR) 12 weeks after the end of therapy. -Treatment discontinuation due to adverse events.	-At 12 weeks, the rates of SVR for patients receiving 12 weeks of sofosbuvir-ribavirin and those receiving 24 weeks of peginterferon-ribavirin were each 67%. -Treatment discontinuation was uncommon among patients receiving sofosbuvir and ribavirin for 12 weeks (1%) as compared with 11% among patients receiving 24 weeks of peginterferon-ribavirin. -Influenza-like symptoms and fever were reported by 18% of patients receiving interferon versus only 3% of patients receiving sofosbuvir. Depression occurred in 14% and 5% of the peginterferon and sofosbuvir groups, respectively.	-In this trial of previously untreated patients with genotype 2 or 3 HCV infection, the rate of sustained virologic response at 12 weeks was the same among patients assigned to receive 12 weeks of sofosbuvir-ribavirin and those assigned to receive 24 weeks of PEG-IFN-ribavirin. Adverse events were less frequent with sofosbuvir than with peginterferon.
Kowdley et al[125] 2014 **LOE-2**	Multicenter, randomized, open-label, phase 3 study (ION-3)	N=647	-Adult subjects ≥18 years of age with chronic HCV genotype 1 infection	-The sustained virologic response (SVR) rate at 12 weeks after the end of therapy	-The primary endpoint results, SVR, were as follows: 94% (N=202/215) with group 1, 93% (N=201/216) with group 2, and 95% (N=206/216) with group 3.	-In this population with HCV genotype 1 infection without cirrhosis who had not previously been

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	ledipasvir/ sofosbuvir (l/s) QD x8W (group1) Vs l/s plus ribavirin QD X8W (group2) Vs l/s QD X12W (group3)	8-12 weeks	without cirrhosis who had not received treatment for HC V infection previously	-Non-inferiority of treatment arms and virologic relapse were also assessed -Safety	The criteria were met for all 3 groups, with rates of SVR that were superior to the adjusted historical control rate of 60% ($p<0.001$ for all comparisons). -The SVR rate of group 1 was non-inferior to the response rates of the other groups. -Of the total group, none had virologic breakthrough during the study; however, 23 had virologic relapse after the end of treatment: 5% (N=11) in group 1, 4% (N=9) in group2 and 1% (N=3) in group 3. -There were 3 discontinuations of treatment due to adverse events: 1 in group 2 and 2 in group 3. -Fatigue, headache, and nausea were the most frequently reported adverse events.	treated, there was a high rate of SVR associated with ledipasvir/sofosbuvir treatment for 8 weeks.
Afdhal et al[126] 2014 **LOE-2**	Multicenter, randomized, open-label, phase 3 study (ION-1)	N=865	-Adult subjects ≥18 years of age with chronic HCV genotype 1 infection and had not	-SVR rate at 12 weeks after the end of treatment -Virologic relapse	-The primary endpoint results, SVR, were as follows: 99% (N=211/214) with group 1, 97% (N=211/217) with group 2, 98% (N=212/217) with group 3, and 99% (N=215/217). The rates of	-Once daily ledipasvir/ sofosbuvir combination, with or without ribavirin, was highly

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	ledipasvir/ sofosbuvir (l/s) QD X12W (Group1) Vs l/s plus ribavirin X12W (Group 2) Vs l/s QD X24W (Group 3) Vs l/s plus ribavirin X24W (Group 4)	12-24 weeks of treatment	received prior HCV treatment	-Safety	SVR in all 4 treatment groups were superior to the historical rate of 60% (p<0.001 for all comparisons). -Overall, there were only with virologic failure: 1 in the group 3 with virologic breakthrough during treatment and 2 with virologic relapse. Of those with virologic relapse, 1 was in group 1 and one was in group 3. -There were no discontinuations of treatment due to adverse events in either 12-week treatment group; however, there were 10 who discontinued treatment due to adverse events between the two 24-week treatment groups. These included 4 in group 3 and 6 in group 4. -At least 79-92% had ≥1 adverse event (AE). The most frequently reported AEs included fatigue, headache, insomnia, and nausea.	effective in this population of previously untreated patients with HCV genotype 1 infection.
Afdhal et al[127] 2014 **LOE-2**	Multicenter, randomized, open-label, phase 3 study (ION-2)	N=400	-Adult subjects ≥18 years of age who had chronic HCV genotype 1 infection and	-The SVR rate at 12 weeks after the end of treatment -Virologic relapse	- The primary endpoint results, SVR, were as follows: 94% (N=102/109) with group 1, 96% (N=107/111) with group 2, 99% (N=108/109) with group 3, and	-High rates of SVR in this population with HCV genotype 1 infection who had not sustained

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	ledipasvir/ sofosbuvir (l/s) QD X12W (group 1) Vs l/s plus ribavirin X12W (group2) Vs l/s QD X24W (group3) Vs l/s plus ribavirin X24W (group4)	12-24 weeks	who had not sustained virologic response with either PEG-IFN and ribavirin with or without a protease inhibitor (PI)	-Safety	99% (N=110/111) with group 4. The rates of SVR in all 4 treatment groups were superior to the adjusted historical response rates of 25% (p<0.001 for all comparisons). -Overall, 2% had a virologic relapse after the end of treatment: 7 (6%) from group 1 and 4 from group 2. There were no patients from the 24W treatment arms that had a virologic relapse. -The majority in each treatment group (67-90%) reported adverse events, most of which were mold to moderate in severity. -There were no discontinuations due to adverse events.	virologic response to prior interferon treatment was seen with ledipasvir/ sofosbuvir combination.
Andreone et al[128] 2014 **LOE - 2**	Multicenter, open-label phase 3 trial	N = 179	- Adults aged 18-70 years who previously failed treatment with pegIFN/RBV - Noncirrhotic with chronic HCV genotype 1b infection for	- Non-inferiority - Decrease in hemoglobin levels - Superiority to the historical rate for telaprevir plus pegIFN/RBV	- After 12 weeks of treatment, 96.6% (85 of 88; 95% CI, 92.8–100) of group 1 and 100% (91 of 91; 95% CI, 95.9–100) of group 2 patients achieved SVR12 using the intent-to-treat population for both groups. - SVR12 rates in both treatment	- ABT-450/ritonavir/ ombitasvir and dasabuvir without RBV is sufficient to achieve optimal treatment of HCV genotype 1b infection in this

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	ABt-450 (paritaprevir)/ ritonavir/ ombitasvir (150/100/25 mg QD) and dasabuvir (250 mg BID) & RBV (1000 mg if < 75 kg or 1200 mg if ≥ 75 kg (group 1) Vs without RBV (group 2)	12 weeks	at least 6 months with an HCV-RNA level > 10,000 IU/mL	- Noninferiority of group 1 and 2 for the historical SVR12 difference	groups were non-inferior to the historical SVR rate for telaprevir plus pegIFN/RBV in comparable treatment-experienced patients. - Both treatment groups also were superior to the historical rate. - Noninferiority of group 2 to group 1 was shown because the treatment difference in SVR12 rates was 3.4%	population.
Feld et al[129] 2014 **LOE-1b**	Multicenter, randomized, double-blind, placebo-controlled trial ABT-450/r-ombitasvir 150 mg QD, ritonavir 100 mg QD, dasabuvir 250 mg BID, and ribavirin (weight-based dosing QD) Vs placebo	N = 631 12 weeks	- Adults ages 18-70 with chronic HCV genotype 1 infection, no cirrhosis, and a plasma HCV RNA level of more than 10,000 IU per milliliter, who had never received antiviral treatment for HCV infection. Without HIV or HBV	- Sustained virologic response (HCV RNA level <25 IU per milliliter) at 12 weeks - Normalization of the alanine aminotransferase (ALT) level, sustained virologic response at post-treatment week 12 according to HCV genotype (1a or 1b), virologic failure during treatment, and post-treatment relapse	- Rate of sustained virologic response at post-treatment week 12 were 95.3% (95% CI, 93.0 to 97.6) among patients with HCV genotype 1a infection (307 of 322 patients) and 98.0% (95% CI, 95.8 to 100) among those with HCV genotype 1b infection (148 of 151). - Rate of normalization of the alanine aminotransferase level was 97.0% in group A (352 of 363 patients), as compared with 14.9% in group B (17 of 114; p<0.001).	- A multi-targeted approach combining the direct-acting antiviral agents ABT- 450/r–ombitasvir and dasabuvir with ribavirin was associated with a high rate of sustained virologic response at post-treatment week 12, with a low rate of treatment discontinuation, among previously untreated patients

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						with HCV genotype 1 infection and no cirrhosis.
Poordad et al[130] 2014 **LOE-2**	Randomized, open-label trial ABT-450/r–ombitasvir 150 mg QD, 100 mg of ritonavir 100 mg QD, ombitasvir 25 mg QD and dasabuvir 250 mg BID with ribavirin (1000 mg or 1200 mg daily, according to body weight, in two doses) for 12 weeks Vs for 24 weeks	N = 380 12 or 24 weeks	- Adults aged 18-70 years previously untreated or previously treated chronic HCV genotype 1 infection and a plasma HCV RNA level of more than 10,000 IU per milliliter	- Sustained virologic response (an HCV RNA level of <25 IU per milliliter) 12 weeks after the end of study-drug administration and non-inferiority - Percentage of patients in each group with virologic failure during treatment or relapse after treatment	- 191 of 208 patients who received 12 weeks of treatment had a sustained virologic response at post-treatment week 12, for a rate of 91.8% (97.5% CI, 87.6 to 96.1). A total of 165 of 172 patients who received 24 weeks of treatment had a sustained virologic response at post-treatment week 12, for a rate of 95.9% (97.5% CI, 92.6 to 99.3). - Met non-inferiority criteria.	- Combining ritonavir-enhanced ABT-450 with ombitasvir, dasabuvir, and ribavirin resulted in rates of SVR at post-treatment week 12 of 92% with a 12-week regimen and 96% with a 24-week regimen, with a low rate of treatment discontinuation, among both previously untreated and previously treated patients with HCV genotype 1 infection and compensated cirrhosis, a group at risk for liver-related illness and death

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						CHC Comments: Internal study validity limited due to lack of blinding.
Sulkowski et al[131] 2015 **LOE - 2**	Randomized, open-label study ombitasvir/ paritaprevir/r, dasabuvir, and ribavirin for 12 or 24 weeks	N = 63 12 or 24 weeks	-Adults aged 18-70 with HCV genotype 1 and HIV-1 infection, had plasma HCV RNA > 10 000 IU/mL, and were either HCV treatment-naïve or previously treated with pegIFN plus ribavirin	- HCV sustained virologic response at posttreatment week 12 (SVR12) - Comparisons of SVR12 rates between the 12- and 24-week treatment groups	- 58 of 63 patients (92%) had an HCV RNA < 10,000 IU/mL at week 2, and all patients achieved rapid HCV RNA suppression by treatment week 4. -After 12 or 24 weeks of treatment with 3D plus ribavirin, 29 of 31 patients (94%; 95% CI, 79%-98%) and 29 of 32 patients (91%; 95% CI, 76%-97%) achieved SVR12 (P > 0.99).	- Treatment with the all-oral, IFN-free 3D-plus-ribavirin regimen resulted in high SVR rates among patients co-infected with HCV genotype 1 and HIV-1 whether treated for 12 or 24weeks. Further phase 3 studies of this regimen are warranted in co-infected patients **CHC Comments:** Internal study validity limited due to lack of blinding.
Ferrenci et al[132] 2014 **LOE-1a**	Two randomized, double-blind, placebo-controlled	N = 419	- Adults aged 18-70 years with chronic HCV genotype 1 infection with an HCV RNA	- SVR (HCV RNA <25 IU/mL) 12 weeks after the end of treatment to assess the non-inferiority of the rate of sustained	- At post-treatment week 12, genotype 1a study, 97 of 100 patients who received the antiviral regimen with ribavirin had a SVR at post-treatment week 12, for a rate of 97.0% (95% CI, 93.7 to	- Previously untreated patients with HCV genotype 1a or 1b infection and no cirrhosis who received ABT-

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	ABT-450/r–ombitasvir 150 mg QD, ritonavir 100 mg QD, ombitasvir 25 mg QD and dasabuvir 250 mg BID with or without weight-based ribavirin	12 weeks	level of more than 10,000 IU per milliliter and had never received any antiviral treatment for HCV - One trial looked at genotype 1a and the other looked at 1b	virologic response at post-treatment week 12 in each study group, as compared with the historical rate with telaprevir plus peginterferon–ribavirin - Non-inferiority	100); 185 of 205 patients who received the regimen without ribavirin had a sustained virologic response, for a rate of 90.2% (95% CI, 86.2 to 94.3). - At post-treatment week 12, genotype 1 b had an SVR for a rate of 99.5% (95% CI, 98.6 to 100.0); 207 of the 209 patients who received the regimen without ribavirin had a sustained virologic response, for a rate of 99.0% (95% CI, 97.7 to 100.0). - Both were non-inferior and superior to the historical rate.	450/r–ombitasvir and dasabuvir with or without ribavirin had high sustained-virologic-response rates that were superior to the historical response rate with peginterferon–ribavirin plus telaprevir. Although ribavirin did not improve the response in patients with genotype 1b infection, our findings suggest that ribavirin confers an additional benefit for patients with genotype 1a infection.
Zeuzem et al[133] 2014 **LOE-1b**	Randomized, double-blind, placebo-controlled phase 3 trial	N = 394	- Adults 18 – 70 years old with chronic HCV genotype 1 infection and a plasma HCV	- Sustained virologic response (HCV RNA <25 IU per milliliter at week 12 - Normalization of	- 98.7% had an HCV RNA level of less than 25 IU per milliliter at treatment week 4 (95% CI, 97.3 to 100); 99.0% had an HCV RNA level of less than 25 IU per milliliter at treatment	- An all-oral combination regimen of ABT-450/r, ombitasvir, and dasabuvir with ribavirin resulted in

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	ABT-450/r–ombitasvir 150 mg QD, ritonavir 100 mg QD, ombitasvir mg, and dasabuvir 250 mg BID with ribavirin (weight-based) Vs placebo	12 weeks	RNA level of more than 10,000 IU per milliliter, without cirrhosis and with prior pegINF/RBV therapy with relapse	the ALT level - Sustained virologic response at post-treatment week 12 according to HCV genotype (1a or 1b)	week 12 (95% CI, 97.9 to 100). - 286 patients in the active-regimen group had a sustained virologic response at post-treatment week 12, for an overall rate of 96.3% (95% CI, 94.2 to 98.4) and were noninferior and superior to the historical control rate with telaprevir and peginterferon–ribavirin. - Rate of normalization of the ALT level was significantly higher in the active-regimen group than in the placebo group (96.9% [217 of 224 patients] vs. 12.8% [10 of 78 patients], P<0.001).	rates of sustained virologic response at post-treatment week 12 of more than 95%, regardless of HCV genotype (1a or 1b) and with low rates of treatment discontinuation, in previously treated patients with HCV genotype 1 infection and no cirrhosis, including those with a prior null response.
Aqel et al[134] 2015 **LOE-2**	Multicenter, retrospective review Oral regimens including simeprevir / sofosbuvir with or w/out ribavirin	N = 119 12 weeks	- Patients with HCV genotype 1 with compensated cirrhosis and those valuated for LT were considered for treatment	- Proportion of patients who achieved undetected HCV RNA or SVR 12 weeks after completing treatment	-SVR12 was achieved in 78% of patients. - On-treatment viral kinetics, SVR4, and SVR12 were similar between the 24 patients who received RBV, compared with the remaining 95 patients who did not receive RBV.	- SVR12 was lower in patients with more advanced liver disease which supports the FDA recommendation to extend duration of therapy of SMV/SOF to 24 weeks in patients with cirrhosis

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Charlton et al[136] 2015 LOE - 2	Multi-center, open-label study sofosbuvir 400 mg and ribavirin 200–1200 mg PO QD	N = 40 24 weeks	- Adults with chronic HCV and HCV RNA ≥ 104 IU/mL, and had received a liver transplant	- Percentage of subjects with SVR12, defined as HCV RNA < 25 IU/mL 12 weeks post-treatment	- 28 (70%, 90% CI: 56%_82%) achieved SVR12. - All 28 patients who achieved SVR12 also had HCV RNA plasma concentration below the LLOQ at 24 weeks after stopping therapy.	- Treatment with the all-oral regimen of sofosbuvir and ribavirin for 24 weeks resulted in an SVR rate of 70% among patients who experienced recurrence of HCV infection after liver transplantation
Mizokami et al[137] 2015 LOE - 2	Multicenter, randomized, open-label study ledipasvir 90 mg and sofosbuvir 400 mg Vs ledipasvir, sofosbuvir, and ribavirin (weight-based)	N = 341 12 weeks	- Adults ≥ 20 years with chronic genotype 1 HCV infection with serum hepatitis C virus RNA concentrations of at least 5 log10 IU/mL and creatinine clearance of at least 1.0 mL/s	- Proportion of patients who achieved SVR12 - Proportion of patients who attained sustained virological response at 4 and 24 weeks after end of therapy (SVR4 and SVR24)	- 338 (99%) of 341 patients achieved SVR12, including all 171 patients (100%) receiving ledipasvir-sofosbuvir (95% CI 98–100) and 167 (98%) of the 170 patients receiving ledipasvir-sofosbuvir plus ribavirin. - Identical number of patients for SVR4 and SVR 24.	- The all-oral, interferon-free and ribavirin-free fixed-dose combination of ledipasvir and sofosbuvir given as one tablet once daily might be an important advancement in the treatment of hepatitis C virus genotype 1 in Japan.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Pol et al[138] 2015 **LOE- 2**	Multicenter, open-label study sofosbuvir 400mg plus PEG-IFN-a 180ug/week, and ribavirin (weight-based) after failing previous direct-acting anti-viral	N = 80 12 weeks	- Adults with chronic genotype 1 HCV infection who did not achieve SVR after treatment in one of seven clinical trials of regimens containing one of Gilead's first-generation investigational protease inhibitors	- Proportion of patients who achieved SVR12 (HCV RNA level <25 IU per milliliter)	- 63 (79%) of 80 patients achieved SVR12 (95% CI: 67-87)	- Patients without cirrhosis who did not achieve SVR after treatment with DAA combinations including a protease inhibitor and RBV with or without Peg-IFN achieved high rates of SVR12 when retreated with Peg-IFN, RBV, and sofosbuvir.
Bourliere et al[139] 2015 **LOE-1b**	Randomized, multicenter, double-blind, placebo-controlled phase 2 study ledipasvir 90 mg, sofosbuvir 400 mg, and ribavirin X12W Vs ledipasvir, sofosbuvir, and placebo X24W	N = 155 12 vs. 24 weeks	- Adults with HCV genotype 1 infection and cirrhosis and had not achieved SVR after being treated first with peginterferon and ribavirin and then with protease inhibitor plus	- Proportion of patients who achieved SVR12 (HCV RNA level <25 IU per milliliter) at 12 weeks following treatment	- 74 (96%) of patients receiving ledipasvir-sofosbuvir-ribavirin (95% CI 89-99) achieved SVR12, and 75 (97%) of patients receiving ledipasvir-sofosbuvir-placebo (95% CI 91-99) achieved SVR12.	- Patients with HCV genotype 1 who were previous non-responders achieved similar rates of SVR12 whether receiving ledipasvir-sofosbuvir plus ribavirin for 12 weeks versus ledipasvir-sofosbuvir for 24 weeks and

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			interferon and ribavirin			therefore a shorter treatment duration may be beneficial in treatment-experienced patients.
Molina et al[140] 2015 **LOE- 2**	Open-label, non-randomized, uncontrolled, multicenter phase 3 study sofosbuvir 400mg and ribavirin (weight based)	N = 275 24 weeks (12 weeks in treatment naïve patients with genotype 2)	- Adults with chronic HCV genotypes 1-4 infection (including patients with compensated cirrhosis) who are co-infected with stable HIV	- Proportion of patients who achieved SVR 12 (HCV RNA level <25 IU per milliliter) 12 weeks after treatment	- The primary endpoint analysis (intention-to-treat) of treatment-naïve patients achieving SVR12 were as follows: 95/112 (85%) of patients with genotype 1 (95% CI 77-91), 17/19 (89%) with genotype 2 (95% CI 67-99), 52/57 (91%) with genotype 3 (95% CI 81-97), and 26/31 (84%) with genotype 4 (95% CI 66-95). -Of the treatment-experienced patients, the proportion of patients achieving SVR12 was as follows: 5/6 (83%) with genotype 2 (95% CI 36-100), and 42/49 (86%) with genotype 3 (95% CI 73-94).	- Patients with HCV infection genotypes 1-4 who were coinfected with HIV achieved high rates of SVR12 regardless of genotype.
Lawitz et al[141] 2015 **LOE - 2**	Open-label, non-randomized, uncontrolled, single-center phase 2 study	N = 47	- Adults with HCV genotype 2 or 3 infection and HCV RNA levels $\geq 10^4$ IU/mL at screening. All	- Proportion of patients who achieved SVR 12 (HCV RNA level < LLOQ) at 12 weeks after cessation of treatment	- 42/47 (89%) of all patients achieved SVR 12 (95% CI 77-97) - 22/23 (96%) of patients with genotype 2 achieved SVR 12 (95% CI 78-100) versus 20/24 (83%) of patients with genotype 3 (95% CI	- Patients with HCV genotypes 2 and 3 infection with or without cirrhosis who are treatment-experienced achieved high SVR

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	sofosbuvir 400mg, PEG-Interferon (180ug/week), and ribavirin (weight-based)	12 weeks	patients with treatment experienced, defined as patients who experienced virologic failure after previous course of interferon and ribavirin		63-95)	rates.
Charlton et al[142] 2015 **LOE - 2**	Prospective, multicenter, open-label, pilot study sofosbuvir 400 and ribavirin (weight based)	N = 40 24 weeks	- Adults with compensated, recurrent HCV infection of any genotype after primary or secondary liver transplantation	- Proportion of patients who achieved SVR12 (HCV RNA level < 25 IU/mL) 12 weeks after cessation of treatment	- 28/40 (70%) of patients achieved SVR12 (90% CI 56-82). - All patients who achieved SVR12, continued to have response 24 weeks after cessation of therapy.	-Sofosbuvir and ribavirin combination were effective in achieving high rates of SVR12 after 24 weeks of therapy in a difficult-to-treat population. **CHC Comments:** No comparator group, relatively small sample size.
Omata et al[144] 2014 **LOE - 2**	Multicenter, open-label, phase 3 study sofosbuvir 400mg and ribavirin (weight based)	N = 153 12 weeks	- Adults with HCV genotype 2 with HCV RNA levels $\geq 10^4$ IU/mL at screening.	- Proportion of patients achieving SVR12 (HCV RNA level <25 IU/mL) 12 weeks after cessation of treatment	- 148/153 (97%) of all patients achieved SVR12 (95% CI 92.5-99). - 88/90 (98%) of patients who were treatment naïve achieved SVR12 (95% CI 92-99) versus	-Sofosbuvir and ribavirin combination for twelve weeks was effective at achieving high rates

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			Patients could be either treatment naïve or experienced.		60/63 (95%) of patients who were previously treated (95% CI 87-99).	of SVR (>95%) in treatment naïve and treatment-experienced Japanese patients with HCV genotype 2, thus providing evidence for interferon-free treatment regimens.
Lawitz et al[145] 2014 **LOE - 2**	Randomized, open-label, multicenter study sofosbuvir 400mg, simeprevir 150mg, with or without ribavirin for 24 weeks (groups 1 and 2) sofosbuvir 400mg, simeprevir 150mg with or without ribavirin for 12 weeks (groups 3 and 4)	N = 168 Group 1 and 2: 24 weeks Group 3 and 4: 12 weeks	- Adults with HCV genotype 1 infections who had previously not responded to treatment with PEG-IFN plus ribavirin or treatment naïve	- Proportion of patients achieving SVR12 (HCV RNA level <25 IU/mL) 12 weeks after stopping treatment	- 154/168 (92%) of patients achieved SVR12 overall (95% CI 81 – 96 in cohort 1 and 95% CI 87-98 in cohort 2) -SVR rates were similar when comparing 12 weeks versus 24 weeks of therapy, nor were any differences noted in patients receiving ribavirin versus placebo	Sofosbuvir and simeprevir combinations are effective in achieving high rates of SVR in patients with HCV genotype 1 who were previously treated with similar rates seen whether ribavirin was added. **CHC Comments:** Open-label study design, small number of patients per treatment group, and

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						inadequate statistical power to detect differences between treatment groups
Sulkowski et al[146] 2014 **LOE - 2**	Non-randomized, open-label, uncontrolled, multicenter phase 3 study sofosbuvir 400mg and ribavirin (weight based)	N = 223 12 weeks (24 weeks in treatment-experienced patients with genotype 2 or 3, and patients with genotype 1)	- Adults with HCV genotype 1, 2 or 3 and concurrent HIV infection. Patients were required to be receiving ART with controlled HIV disease (RNA values of less than 50 copies/mL or CD4 T cell count of more than 200 cells/uL)	- Proportion of patients achieving SVR12 (<25 copies/mL) 12 weeks after cessation of HCV therapy	- Treatment naïve patients: 87/114 (76%) with genotype 1 (95% CI 67-84), 23/26 (88%) with genotype 2 (95% CI 70-98), 28/42 (68%) with genotype 3 (95% CI 51-80) achieved SVR12. - Treatment experienced patients: 22/24 (92%) with genotype 2 (95% CI 73-99), 16/17 (94%) with genotype 3 (95% CI 71-100) achieved SVR12.	-Patients with HCV genotypes 1, 2, or 3 who were coinfected with HIV achieved high rates of SVR12 when given a combination of sofosbuvir and ribavirin without the need for interferon. **CHC Comments:** Low number of patients with cirrhosis (10%), women (17%), or patients with advanced HIV disease (with lower CD4 count). No control groups.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Zeuzem et al[147] 2014 **LOE-2**	Descriptive open-label study sofosbuvir 400mg plus ribavirin (weight-based)	N = 419 12 weeks (24 weeks for patients with genotype 3)	- Adults with HCV genotype 2 or 3 with serum HCV RNA levels of 10,000 IU/mL or higher	- Proportion of patients achieving SVR12 (HCV RNA level <25 IU/mL) 12 weeks after the end of treatment	- 68/73 (93%) of patients with genotype 2 achieved SVR12. - 213/250 (85%) of patients with genotype 3 achieved SVR12 after receiving 24 weeks of treatment.	- Patients with HCV genotypes 2 and 3 achieved high rates of SVR12. **CHC Comments:** Original study design was specified as a placebo-controlled trial for 12 weeks rather than 24 weeks for genotype 3 patients. Study was amended to a descriptive study as opposed to a randomized control trial.
Lawitz et al[148] 2014 **LOE-2**	Single-center, open label, randomized phase 2 study Group 1: sofosbuvir plus ledipasvir Group 2: sofosbuvir plus ledipasvir & RBV Group 3: sofosbuvir and ledipasvir	N = 100 8 weeks for group 1 and 2, 12 weeks for group 3, 4, and 5	- Adults with HCV genotype 1 infection who were treatment naïve	- Proportion of patients achieving SVR12 (HCV RNA level <25 IU/mL) 12 weeks after the end of treatment (intention-to-treat analysis)	- The primary endpoint analysis resulted as follows: Group 1: 19/20 (95%) (95% CI 75-100) Group 2: 21/21 (100%) (95% CI 84-100) Group 3: 18/19 (95%) (95% CI 74-100) Group 4: 18/19 (95%) (95% CI 74-100) Group 5: 21/21 (100%) (95% CI 84-100)	- Patients with HCV genotype 1 achieved high rates of SVR12 with sofosbuvir plus ledipasvir with or without the addition of ribavirin with little difference noted between 8 weeks and 12 weeks of

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	Group 4: sofosbuvir and ledipasvir with prior treatment failure Group 5: sofosbuvir plus ledipasvir & RBV w/prior treatment failure					treatment. **CHC Comments:** Small sample size at a single center. Study was not powered to detect differences in efficacy based on treatment duration.
Ogawa et al[149] 2015 **LOE-2**	Multicenter, open-label, non-randomized, comparative observational study. simeprevir 100mg, PEG-IFNa2b 1.5ug/kg/week, and ribavirin Vs telaprevir 2250mg/day, PEG-IFNa2b 1.5ug/kg/week, and ribavirin	N = 716 24 weeks	- Adults with non-cirrhotic HCV genotype 1b	- Proportion of patients achieving SVR12 (HCV RNA <15 IU/mL)	- 85% of patients receiving simeprevir achieved SVR12 vs. 84.2% of patients achieving SVR12 in the telaprevir group - Higher rates of adverse effects (anemia, severe dermatitis, and nephrotoxicity) were noted in the telaprevir group	- Patients with HCV genotype 1b achieved similar outcomes when receiving triple therapy with either simeprevir or telaprevir in combination with IFNa2b and ribavirin. There were higher rates of adverse effects noted in patients receiving telaprevir-based triple therapy. **CHC Comments:** Observational trial that was not

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						statistically powered, nor designed to detect differences in clinical efficacy. Study was completed in Japan.
Pungpapong et al[150] 2015 **LOE-2**	Multicenter, retrospective study simeprevir 150mg and sofosbuvir 400mg with or without ribavirin (weight-based)	N = 123 12 weeks	- Adults with history of liver transplantation with HCV genotype 1 infection with evidence of HCV recurrence on liver biopsies	- Proportion of patients achieving SVR12 (HCV RNA <10 IU/mL) 12 weeks after completing treatment	- 119/123 (97%) of patients achieved SVR12 (95% CI 94-100) - No difference noted in patients receiving ribavirin (n = 25) - 3 patients discontinued treatment prematurely due to adverse effects	Adult liver transplantation recipients with HCV genotype 1 infection achieved high rates of SVR with mild adverse effects in a multicenter clinical experience report.
Manns et al[151] 2014 **LOE-1b**	Multicenter, randomized, double-blind, placebo-controlled, phase 3 study simeprevir 150mg w/PEG-IFN 2a 180ug/week OR PEG-IFN 2b W/RBV Vs placebo, PEG-IFN 2a or 2b, and ribavirin	N = 391 24 weeks (48 weeks in the simeprevir group)	- Adults with HCV genotype 1 infection who are treatment naïve	- Proportion of patients achieving SVR12 (HCV RNA <25 IU/mL) 12 weeks after completing treatment	- 209/257 (81%) of patients in the simeprevir group achieved SVR12 versus 67/134 (50%) of patients in the placebo group (adjusted difference 32.2%, 95% CI 23.3-41.2; p<0.0001). - No differences noted with either type of peginterferon.	-Adult patients with HCV genotype 1 achieved higher rates of SVR when given simeprevir in combination with PEG-IFN plus ribavirin when compared to placebo with no additional worsening in adverse effects.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Jacobson et al[152] 2014 **LOE-1b**	Multicenter, randomized, double-blind, placebo-controlled, phase 3 study simeprevir 150mg plus RBV 9weight based) followed by PEG-IFN 2a plus ribavirin Vs placebo plus RBV followed by PEG-IFN 2a plus ribavirin	N = 394 24 weeks (48 weeks in the simeprevir group according to criteria for response-guided therapy)	- Adults with chronic HCV genotype 1 infection with no history of prior HCV treatment	- Proportion of patients with SVR12 (HCV RNA <25 IU/mL) 12 weeks after completing treatment	- 210/264 (80%) of patients in the simeprevir group achieved SVR12 versus 65/130 (50%) of patients in the placebo group (adjusted difference 29.3%, 95% CI 29.1-38.6; p<0.0001).	- Adult patients with HCV genotype 1 who were treatment naïve achieved higher rates of SVR12 when receiving simeprevir in comparison to placebo with no additional noted adverse effects. **CHC Comments:** Limited number of patients with cirrhosis limited broad applicability
Forns et al[153] 2014 **LOE-1b**	Randomized, multicenter, double-blind, parallel group, placebo-controlled, phase 3 study simeprevir 150mg plus PEG-IFN a-2a 180ug/week & ribavirin then PEG-IFN and ribavirin Vs	N = 393 24 or 36 weeks (simeprevir/ placebo group based on response guided criteria)	- Adults with HCV genotype 1 infection with screening plasma HCV-RCA levels >10,000 IU/mL who had relapsed after 24 weeks or more of IFN-based therapy. Confirmatory	- Proportion of patients achieving SVR12 (HCV RNA < 25IU/mL) 12 weeks after planned end of therapy	- 206/260 (79.2%) of patients in the simeprevir group achieved SVR12 versus 48/133 (36.1%) in the placebo group (difference of 43.8%, 95% CI 34.6 – 53.0; p<0.001). - 92.7% of simeprevir patients met response-guided therapy criteria to complete treatment at week 24.	- Adult patients with HCV genotype 1 who had relapsed after prior interferon-based therapy achieved higher rates of SVR12 when receiving simeprevir in comparison to placebo. Therapy was shortened to

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	placebo plus PEG-IFN a-2a and ribavirin		biopsy was required			24 weeks in most patients receiving simeprevir.
Curry et al[157] 2015 **LOE- 2**	Prospective, open-label, phase 2 pilot study sofosbuvir 400mg and ribavirin (weight-based)	N = 61 Up to 48 weeks prior to liver transplantation (analysis included patients who received any duration of therapy)	- Adults with HCV infection of any genotype and cirrhosis (Child-Turcotte Pugh score, ≤7) who were on waitlists for liver transplantation for hepatocellular carcinoma	- Proportion of patients attaining post-transplantation virologic response (pTVR), defined as HCV-RNA levels less than 25 IU/mL at 12 weeks post-transplantations in patients who had HCV-RNA levels less than LLOQ at their last assessment prior to transplantation	- 61 patients received at least one dose of sofosbuvir and ribavirin and 46 of these patients underwent transplantation - 43/46 patients had HCV RNA < 25 IU/mL at the time of transplantation - 30/43 (70%) patients had a pTVR at 12 weeks following transplantation, 10 (23%) had recurrent infection, and 3 (7%) died - Median duration of exposure of medication was 21 weeks (range, 2.3 – 52.3 weeks) - By the fourth week of treatment, 54 of 58 patients (93%) receiving treatment achieved an HCV RNA less than 25 IU/mL	-Administration of sofosbuvir and ribavirin in the pre-liver transplantation period in patients with active HCV infection was effective and reducing the recurrence of HCV after transplantation. **CHC Comments:** Small size, single centre, and lack of comparator arm do not allow for direct comparisons with other historically used treatments in preventing post-transplantation HCV recurrence. Only patients with hepatocellular carcinoma were

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						included, limiting the applicability of data to other disease states which require liver transplantation.
Nelson et al[161] 2015 **LOE-2**	Phase III, open-label, 2 cohort study daclatasvir (DCV) 60mg plus sofosbuvir (SOF) 500mg QD	N=152 12 weeks, with subsequent 24-week follow-up	-Adult subjects ≥18 years with chronic genotype 3 infection either treatment-naïve or treatment experience	-Co-primary endpoints were proportion of treatment-naive and treatment-experienced achieving sustained virological response (SVR) of SVR12 -Safety	-There were 101 treatment-naïve (TN) subjects and 51 treatment experienced (TE). -SVR12 rates were 90% in the TN cohort and 86% in the TE cohort. -The overall SVR12 rate was 89%. Rapid and sustained reductions from baseline in HCV-RNA levels were see on-treatment weeks 1 and 2. -The proportion achieving HCV-RNA levels <lower limit of quantitation (LLOQ) at early on-treatment time points was 40% for TN and 24% for TE at week 1, 77% and 69%, respectively at weeks 2, and 94% and 98%, respectively at week 4. -SVR23 rates were higher in patients without cirrhosis (96%) than with cirrhosis (63%) for the	-This 12-week treatment regimen of daclatasvir plus sofosbuvir achieved a high SVR12 rate in this population with genotype 3 HCV (96% without cirrhosis), while being well tolerated.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					overall cohort. For the TN cohort, SVR12 rates were 97% without cirrhosis vs 58% with cirrhosis. For the TE cohort, the SVR12 rates were 94% without cirrhosis and 69% with cirrhosis. -5 of 7 patients who previously failed SOF-containing regimens achieved SVR12. -16 patients (9 TN and 7 TE) had post-treatment relapse. -Treatments were well tolerated, with no adverse event (AE) leading to discontinuation of treatment. There were no deaths. -The most frequently reported AEs included headache, fatigue, and nausea.	
Sulkowski et al[162] 2014 **LOE-2**	Open-label study	N=211	-Adult subjects 18-70 years with chronic HCV genotype 1, 2, or 3 with no evidence of cirrhosis, and patients with prior treatment	-The proportion with an SVR at week 12 after the end of treatment -Safety	-Patients with genotype 1 were assigned to group A, C, or E and patients infected with genotype 2 and 3 were assigned to group B, D, or F. -Among patients with genotype 1 infection, 98% of previously 126 untreated patients and 98% of 41	-Daclatasvir plus sofosbuvir was associated with high rates of SVR among patients infected with genotype 1,2, or 3, while being well tolerated.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	sofosbuvir X1W then daclatasvir plus SOF X23W (group A and B) Vs DAC plus SOF X24W (group C & D) Vs DAC plus SOF plus RBV X24W (group E & F)	24 weeks	had confirmed virologic failure during or after treatment w/telaprevir or boceprevir plus PEG/RBV		patients who did not have an SVR with protease inhibitors had an SVR at week 12 after the end of therapy. -92% of 26 patients with genotype 2 and 89% of 18 patients with genotype 3 had SVR at week 12. -Virologic relapse was confirmed in 1 patient with genotype 3 who received treatment without RBV. -The most commonly reported adverse events included fatigue, headache, and nausea.	
Hezode et al[163] 2015 **LOE-2**	Multicenter, ongoing phase 2b, randomized, open-label study (PEARL-I) ombitasvir/ paritaprevir/ ritonavir (o/p/r) plus ribavirin Vs o/p/r (no ribavirin)	N=135 12 weeks	-Adult subjects aged 18-70 years with chronic HCV genotype 4 infection who were non-cirrhotic; patients were treatment-naïve or had previously	-SVR12 -Post-treatment relapse and on-treatment virological failure -Safety	-In treatment-naïve patients, SVR12 rates were 100% in the RBV group and 90.9% in the RBV-free regimen. Statistically significant differences in SVR12 rates between these groups were not seen (p=0.086). -100% of treatment-experienced patients in the RBV group achieved SVR12. -No relapses between post treatment week 12 and post treatment week 24 were recorded	-An interferon-free regimen of ombitasvir plus paritaprevir plus ritonavir, with or without ribavirin, achieved high SVR at 12 weeks after the end of treatment, while being well tolerated.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					in treatment naïve patients. -3 treatment-naïve not taking ribavirin had virologic failure. There were no virologic failures in the ribavirin group. -The most common treatment-emergent adverse events were headache, asthenia, fatigue, insomnia, and nausea.	
Buti et al[186] 2016 **LOE-2**	Open-label, prospective trial grazoprevir 100mg PO QD, elbasvir 50 mg QD and ribavirin PO BID at a daily dose of 800-1400 mg for 12 weeks	N=79 Follow-up: 36 weeks	-Adults with chronic HCV genotype 1 infection who had already failed 4 or more weeks of combined boceprevir, telaprevir or simeprevir.	- Plasma HCV RNA measurements were to be performed at posttherapy follow-up weeks 4, 8, 12, and 24. Success at follow-up visits was defined as HCV RNA levels below the assay limit of quantification (15 IU/mL).	- At the end of therapy, HCV RNA was undetectable in 78 of 79 (98.7%) patients; the only subject with detectable HCV RNA below the assay limit of quantification relapsed by follow-up week 4. Overall, relapses occurred in 3 (3.8%) patients (2 with genotype 1a and 1 with genotype 1b infection) within the first 8 weeks after cessation of study therapy (2 at follow-up week 4 and 1 at follow-up week 8), yielding an SVR12 rate of 96.2% (95% confidence interval [CI], 89.3%–99.2%). -Undetectable HCV RNA levels were maintained throughout the full 24 weeks of follow-up in the	-In this study, 79 patients with chronic HCV genotype 1 infection who had failed earlier PI-based combination regimens were treated with grazoprevir and elbasvir plus ribavirin, including 84% with past history of virologic failure. The combination of grazoprevir and elbasvir with ribavirin given orally for 12 weeks

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					other 76 patients. Thus, SVR24 was attained in 76 of 79 patients (96.2% [95% CI, 89.3%–99.2%]) overall, in 28 of 30 (93.3%) patients with genotype 1a infection, 63 of 66 (95.5%) patients with prior virologic failure, 33 of 36 (91.7%) patients with baseline NS3 and/or NS5 RAVs, and 32 of 34 (94.1%) patients with cirrhosis.	offers a new therapeutic option for patients who have failed treatment.
Naggie et al[181] 2015 **LOE-2**	Multicenter, single group, open label trial ledipasvir 90 mg + sofosbuvir 400mg QD	N=335 12 weeks	-Adults stable on antiretroviral medication for HIV-1 for ≥ 8 weeks, have HIV-1 viral suppression with a CD4+ count of > 100 cell/µL, and CrCl ≥ 60 mL/min	-Rate of sustained virologic response, defined as the absence of quantifiable HCV RNA in serum (<25 IU/mL) at 12 weeks after the end of therapy.	-Among the 335 patients who were enrolled and treated, 322 (96%; 95% confidence interval [CI], 93 to 98) had a sustained virologic response 12 weeks after the end of therapy. Of the 322 patients with a response, 312 returned for the post-treatment week 24 visit, at which all the patients had a sustained virologic response. -The rates of response at 12 weeks were similar in patients with genotype 1a and those with 1b, in men and women, in patients who had undergone previous treatment and those who had not, in patients receiving various concomitant HIV antiretroviral	-A fixed-dose combination of ledipasvir plus sofosbuvir for 12 weeks provided high rates of sustained virologic response in patients with HCV genotype 1 or 4 who were coinfected with HIV-1, including those who had previous treatment failure while receiving regimens that included direct-acting antiviral drugs and

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					regimens, and in patients with cirrhosis (including those who had received previous treatment) and those without cirrhosis. -Black patients had lower response rates than did patients of other races (90% [95% CI, 83 to 95] vs. 99% [95% CI, 97 to 100], P<0.001 by Fisher's exact test). - All 13 patients who had a relapse after completing 12 or 24 weeks of previous treatment with sofosbuvir plus ribavirin had a sustained virologic response. -In total, 13 patients (4%) did not have a sustained virologic response. Of these patients, 1 died after 4 weeks of treatment, 2 had HCV breakthrough during treatment that was associated with suspected poor adherence (either on the basis of a low study-drug concentration or an investigator report), and 10 had an HCV relapse. All 10 patients with a virologic relapse were black, 7 had the TT allele in the gene encoding IL28B (which	those with cirrhosis. Response rates in the study were similar to those seen in the phase 3 registration trials for this regimen in HCV-mono-infected patients.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					confers an increased risk of treatment failure with interferon-containing regimens), and 8 received efavirenz. -To identify which of these characteristics were associated with HCV relapse, exploratory univariate analysis was performed, which identified black race and the presence of the TT allele as significant associations. -Although among black patients, relapses occurred in 8 of 61 patients taking efavirenz (13%) and in 2 of 54 patients taking other antiretroviral regimens (4%), the difference was not significant (P=0.10). In the multivariate analysis, black race was the only factor that had an independent association with relapse (odds ratio, 17.73; P=0.001).	
Pearlman et al[179] 2015 **LOE-2**	Prospective, randomized open-label study	N=82	-Adults (≥18 years old) who had genotype 1a infection, a plasma HCV-RNA level > 10,000 IU/mL,	-Proportion of patients with SVR12	-All patients in both arms had quick and sustained decreases in serum HCV-RNA levels through the end of therapy. By week 2, 88% in the interferon-containing arm and 71% in the all-oral therapy arm had HCV-RNA levels	-In a population of genotype 1a–infected patients with compensated cirrhosis, both treatment-naive and prior null

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	simeprevir 150mg QD + sofosbuvir 400mg QD Vs peginterferon alfa-2b (1.5 mcg/kg/wk) + oral ribavirin (1000-1200 mg/day base on body weight) + sofosbuvir 400mg QD	12 weeks	and documented cirrhosis		less than 25 IU/mL; 12% and 29%, respectively, had quantifiable virus. Although at week four 96% of patients in the interferon-containing arm had undetected serum virus, only 81% of patients in the all-oral therapy arm achieved this response. Four percent and 19%, respectively, had detectable virus. -Nonetheless, all patients who did not achieve undetectable HCV-RNA levels at week 4 in either arm still achieved SVR12; there was no correlation with the rapidity of viral decrease and the study's primary end point. There was no statistical difference in viral load at week 2 or at week 4 between patients who achieved SVR12 vs those who did not (*P* = NS for both comparisons). -No patients had a viral breakthrough at any point in therapy. -At week 8, 7% of patients in the simeprevir and sofosbuvir arm and none of the patients in the	responders to peginterferon/ribavirin, the all-oral regimen of simeprevir and sofosbuvir showed significantly better sustained virologic response rates, a lesser rate of virologic relapse, and was better tolerated in terms of patient-reported outcomes and adverse events than a peginterferon containing regimen including ribavirin and sofosbuvir when both were administered for 12 weeks. Efficacy was similar irrespective of subject ethnicity.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					interferon-containing arm had detectable serum virus. In the treatment-naive patients in the simeprevir and sofosbuvir arm, 1 patient was lost to follow-up evaluation, and no patient relapsed. However, 3 patients in the null responder group who were treated with simeprevir and sofosbuvir had a virologic relapse (3 of 36; 8%). -The overall SVR rate for the all-oral therapy arm was 54 of 58 (93%, vs 18 of 24 [75%] for the interferon arm; *P* = .02). A total of 3 patients relapsed in the interferon-containing arm, 1 in the treatment-naive group and 2 in the null group, with an overall SVR rate for this arm of 75% (18 of 24). -Three patients withdrew because of adverse events and were included as treatment failures in the intention-to-treat analysis. There was a statistically higher rate of relapse in the interferon-containing arm vs the all-oral therapy arm (P = .009). There were no significant differences in	

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					outcome by race or by prior response.	
Poordad et al[166] 2016 **LOE-2**	Prospective, phase 3, open-label, two parallel cohort study daclatasvir 60mg QD + sofosbuvir 400mg QD + ribavirin 600 mg/day (with potential to increase to 1000 mg/day bases on Hgb and CrCl)	N=120 12 weeks treatment + followed 24 weeks post treatment	-Treatment-naïve or treatment-experienced adults infected with HCV genotype 1-6 with HCV RNA levels at least 10,000 IU/mL. Cohort 1: HCV-associated cirrhosis and potential need for future liver transplant. Cohort 2: HCV recurrence after liver transplant.	- HCV RNA below 25 IU/mL after post-treatment week 12 (SVR12) among genotype 1-infected patients	-In the overall study population, 50 of 60 patients (83%; 95% CI, 71.5%-91.7%) in the advanced cirrhosis cohort and 50 of 53 patients (94%; 95% CI, 84.3%-98.8%) in the posttransplantation cohort achieved SVR12. SVR12 in patients with genotype 1 infection, the primary study endpoint, was achieved by 37 of 45 patients (82%; 95% CI, 67.9%-92.0%) in the advanced cirrhosis cohort and by 39 of 41 patients (95%; 95% CI, 83.5%-99.4%) in the posttransplantation cohort. -All four patients in the advanced cirrhosis cohort who underwent liver transplantation achieved SVR12. One of these patients (genotype 1a) was treated for only one day before receiving a transplant from an HCV genotype 1a-infected donor, and then received an additional 12 weeks of therapy beginning immediately posttransplantation. -HCV RNA levels decreased rapidly	-In conclusion, 12 weeks of oral treatment with the combination of daclatasvir with sofosbuvir and ribavirin achieved high SVR rates across multiple HCV genotypes in high-risk patients with posttransplantation recurrence or Child-Pugh class A or B cirrhosis. Further treatment optimization in patients with Child-Pugh class C disease is required. The regimen was safe and well tolerated, without treatment-limiting pharmacokinetic interactions or toxicities.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					after initiation of treatment in all patients. -At 4 weeks, HCV RNA was below the quantitation limit (25 IU/mL) in 57 of 60 (95%) and 50 of 53 (94%) patients in the advanced cirrhosis and posttransplantation cohorts, respectively, and was undetectable in 32 of 60 (53%) and 30 of 53 (57%) patients. -HCV RNA was undetectable at week 4 in fewer patients with Child-Pugh class C disease (5/15, 33%) than in those with class B (19/31, 61%) or class A (8/12, 67%). Of those who did not achieve SVR12, HCV RNA remained detectable at week 4 in eight of 10 patients in the advanced cirrhosis cohort and in two of three patients in the posttransplantation cohort. However, HCV RNA was undetectable by treatment week 8 or earlier in all 12 patients who relapsed during follow-up. -Twenty-six of 34 (76%) patients in the advanced cirrhosis cohort with	

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					genotype 1a and 11 of 11 (100%) patients with genotype 1b achieved SVR12. Of eight genotype 1a nonresponders, one was Child-Pugh class A, two were class B, and five were class C. -In the post-transplantation cohort, 30 of 31 (97%) patients with genotype 1a and nine of 10 (90%) with genotype 1b achieved SVR12. Overall, 15 of the 17 patients with genotype 3 infection achieved SVR12. All six patients with genotype 3 infection in the advanced cirrhosis cohort had Child-Pugh class B or C disease; five of six (83%) achieved SVR12 and one patient (class C) relapsed. Ten of 11 patients (91%) with genotype 3 infection in the posttransplantation cohort achieved SVR12 and one patient relapsed.	
Roth et al[185] 2015 **LOE-1b**	Multicenter, phase 3, double-blind, randomized study	N=235	-Adults infected with HCV genotype 1 and CKD (stage 4-5)	-Non-randomized comparison of sustained virological response at SVR12 for patients in the immediate treatment group an intensive PK	- Of the 116 remaining patients (immediate treatment group, n=105; intensive pharmacokinetic group, n=11), 115 (99%) achieved SVR12, a rate better than the historical control rate of 45% (p<0·001). One non-cirrhotic	- Results from the C-SURFER study suggested that a once-daily oral regimen of grazoprevir and elbasvir for 12

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	grazoprevir 100mg + elbasvir 50mg QD (12 weeks) Vs placebo (12 weeks) Then, those who initially received placebo received grazoprevir 100mg + elbasvir 50mg QD (12 weeks)	12 weeks ± 12 weeks is initially in placebo group		population vs historical control patient with a reference SVR12 of 45%.	patient with HCV genotype 1b infection and chronic kidney disease stage 5 relapsed 12 weeks after the end of treatment. -In the full analysis set population, 115 (94%) of 122 patients achieved SVR12. Of the seven patients who did not achieve SVR12, six patients discontinued the study for reasons other than virological failure and one patient relapsed. -High response rates were observed in all subgroups, including hemodialysis and non-hemodialysis, and those with characteristics historically associated with poor response to HCV therapy. In particular, SVR12 was achieved in 51 (100%) of 51 African American patients, 86 (99%) of 87 patients with the IL28B non-CC genotype, 40 (98%) of 41 patients with diabetes, and all six patients with cirrhosis. -The SVR24 rate in patients receiving placebo in the deferred treatment group was one (<1%) of	weeks had an acceptable safety profile and could achieve high rates of SVR in patients with HCV genotype 1 infection and advanced chronic kidney disease. The results of this study show that the efficacy and safety profile of this combination is consistent across many patient subgroups, including those receiving hemodialysis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					113. HCV RNA was undetectable in one patient receiving placebo 4 weeks after the end of the placebo treatment period. This patient denied taking any HCV therapy outside the study, had not initiated deferred active therapy, and it was confirmed that the study drug dispensed during the treatment period was placebo.	
Saab et al[180] 2015 **LOE-2**	Randomized, open-label, phase 3, clinical trials (4 studies) ledipasvir 90 mg/Sofosbuvir 400mg QD ± ribavirin BID (weight based)	N=2,293 total 8,12, 24 weeks	-Adults with chronic genotype 1 HCV infection and baseline HCV RNA $\geq 10^4$ IU/mL	-SVR12	-The overall SVR12 in subjects treated with LDV/SOF with or without RBV was 97% (95% CI 96%-98%). The SVR12 was 97% (95% CI 96%-98%) and 98% (95% CI 95%-99%) in subjects <65 years and ≥65 years, respectively. The 24 subjects who were aged ≥75 years had 100% SVR12 (95% CI 86%-100%). The SVR12 among non-Asian and Asian elderly subjects was 96.6% (96.6% CI 92.3%-98.9%) and 99.1% (95% CI 95.2%-100%), respectively. The SVR12 of the 111/112 Asian elderly subjects infected with genotype 1b was 99.1% (95% CI 95.1%-100%). The SVR12 in non-Asian genotype 1a and 1b subjects was 95.5% (95% CI 87.3%-99.1%)	- Whereas in the past age may have been a negative predictor of SVR and associated with increased AEs, the results of this study suggest that LDV/SOF is an effective, tolerable, and safe treatment option for elderly patients with chronic HCV. Elderly patients should not be denied therapy based on an expected lower SVR rate.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					and 97.6% (95% CI 91.5%-99.7%). - Of the elderly subjects who experienced virological failure or had no confirmed virological outcome, three were genotype 1a and three were genotype 1b. One of the subjects (genotype 1b) expired. Baseline NS5A resistance-associated variants (RAVs) were found in three subjects. The percentages of nonelderly and elderly subjects having baseline RS5A RAVS were 17% and 20%, respectively. - The SVR12 in treatment-naive subjects was 97% for those <65 years of age (1454/1506) and 97% (167/172) for those ≥65 years of age. Among treatment-naive subjects without cirrhosis and an HCV RNA <6 million IU/mL treated for 8 weeks with LDV/SOF, 96% (105/109) of those <65 years of age and 100% (14/14) of those ≥65 years of age achieved SVR12. - Treatment-experienced subjects <65 years old achieved an overall SVR12 of 98% (511/523), while the	

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					SVR in subjects ≥65 years old was 99% (91/92). In treatment-experienced subjects ≥65 years old, SVR12 was achieved in 100% (45/45) of subjects who received LDV/SOF for 12 weeks, 97% (30/31) with LDV/SOF+RBV for 12 weeks, 100% (9/9) with LDV/SOF for 24 weeks, and 100% (7/7) with LDV/SOF+RBV for 24 weeks.	
Saxena et al[178] 2015 **LOE-2**	Retrospective, multicenter, cohort study simeprevir 150 mg/sofosbuvir 400mg QD ±ribavirin	N=160 12 weeks	-Genotype 1 HCV-infected adults (≥18 years old) with cirrhosis	-SVR12, defined as an undetectable HCV RNA 12 weeks (± 2 weeks) after completion or early D/C of HCV therapy	- Overall SVR12 frequency was 85%; 73% (40 of 55) in CP (Child-Pugh) B/C patients, and 91% (92/101) in CP-A patients (P < 0.01). Comparing CP-B (n = 49) to CP-C (n = 6) patients, SVR12 frequencies were similar (75% vs. 50%; P = 0.33). -Overall SVR12 frequency among those who received RBV was 89% vs. 82% among those who did not (P = 0.23), 79% (15 of 19) versus 69% (25 of 36) among CP-B/C patients (P = 0.45), and 95% (35 of 37) versus 89% (57 of 64) among CP-A patients (P = 0.35). Among 13 patients previously treated with either telaprevir- or boceprevir-based triple therapy, 10 (77%) achieved SVR12 (6 CP-B/C and 4	- SIM+SOF with and without RBV is highly effective and safe in patients with CP-A cirrhosis but associated with lower SVR rates and higher rates of safety events in patients CP-B/C cirrhosis. However, frequency of safety outcomes was not different than matched untreated controls of similar disease severity, suggesting that these safety events are not related to the drugs per se,

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					CP-A patients). - In univariate analysis, SVR12 was associated with CP-A (vs. CP-B/C), lower baseline bilirubin and MELD, higher baseline albumin and platelets, and absence of any HE or ascites. Use of RBV with SIM+SOF was not associated with SVR12 in univariate analysis (odds ratio [OR]: 1.74; 95% confidence interval [CI]: 0.65-4.68; P = 0.27) nor was previous telaprevir- or boceprevir-based triple therapy experience (OR, 0.45; 95% CI: 0.10-1.94; P = 0.28). -In multivariate models, bilirubin ≥1.3 mg/dL, INR ≥1.3, albumin ≥3.5 g/dL, any HE, any ascites, and MELD were found to be collinear with CP-B/C group (VIF > 10), likely because all either are components or share components of the CP scoring system. Therefore, multivariate model 1 excluded baseline bilirubin, INR, albumin, any HE, any ascites, and MELD. CP-B/C cirrhosis and platelets ≥100 K/mm^3 were factors significantly associated with SVR12 in this	but rather the natural history of decompensated cirrhosis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					model. -In multivariate model 2, where CP-B/C was replaced by its individual components and in this model, albumin ≥3.5 g/dL and platelets ≥100 K/mm^3 were significantly associated with SVR12.	
Kwo et al[173] 2016 **LOE-2**	Multicenter, randomized, open-label study SMV + SOF (simeprevir + sofosbuvir) 12 weeks Vs SMV + SOF 8 weeks	N=310 12 weeks	-HCV (Hep C virus) Genotype 1-Infected Patients Without Cirrhosis	-SVR (sustained virological response) rate 12 weeks after end of treatment (SVR12)	-In the 12-week arm, 70 of 73 (96%) and 80 of 82 (98%) female and male patients achieved SVR 12 weeks after end of treatment (SVR12) versus 62 of 68 (91%) and 66 of 87 (76%), respectively, in the 8-week arm. -SVR12 with simeprevir+sofosbuvir for 12 weeks (97% [150/155; 95% CI 94–100%]) was superior to the historical control (87%). SVR12 with simeprevir+sofosbuvir for 8 weeks (83% [128/155; 95% CI 76–89%]) was not superior to the historical control (83%).	-Using a conventional confidence interval approach and a non-inferiority margin of 12%, non-inferiority of the 8-week versus the 12-week treatment regimen could be concluded.
Lawitz et al[184] 2015 **LOE-2**	Ongoing phase 2b, randomized, open-label, combination treatment study	N= 181	-HCV GT1b infection, 82 pts w/ noncirrhotic and 99 with compensated	-SVR12 (HCV RNA level <25 IU/mL 12 weeks after the last dose of study drug)	-All but 3 patients achieved SVR at week 4, and SVR12 rates were similarly high in patients with and without cirrhosis. SVR12 was achieved in 95.2% (n = 40/42;	-In conclusion, an all-oral interferon- and ribavirin-free regimen of ombitasvir,

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	oral interferon- and ribavirin-free regimen of ombitasvir, paritaprevir, and ritonavir 25 mg/150 mg/100 mg once daily	12 weeks (w/o cirrhosis) 24 weeks (w/cirrhosis)	cirrhosis		95%CI, 83.8%–99.4%) of treatment-naive and 90.0% (n = 36/40; 95% CI, 76.3%–97.2%) of prior null responder patients without cirrhosis. -Among patients with cirrhosis, SVR12 was achieved in 97.9% (n = 46/47; 95% CI, 88.7%–99.9%) of treatment-naive and 96.2% (n = 50/52; 95% CI, 86.8%–99.5%) of treatment-experienced patients	paritaprevir, and ritonavir was generally well tolerated and achieved high rates of SVR12 in both cirrhotic and noncirrhotic patients with HCV GT1b infection who were treatment-naive or treatment experienced, including prior null responders.
Lawitz et al[176] 2015 **LOE-2**	Open label, single-arm, phase 3 study conducted at 35 centers in Canada and the United States oral simeprevir 150 mg once daily + sofosbuvir 400 mg	N= 103 12 weeks	-Chronic HCV GT1 infection and presence of cirrhosis with no suspicion of hepatocellular carcinoma	-To demonstrate superiority of simeprevir + sofosbuvir for 12 weeks versus a historical control (HC) with respect to the proportion of patients achieving SVR12.	-The primary efficacy end point, SVR12, was met by 83% (86/103, 95% CI 76%-91%) of HCV GT1-infected patients with cirrhosis receiving simeprevir 1 sofosbuvir for 12 weeks, and the primary objective of superiority to the HC was achieved (lower limit of the 95% CI of the SVR12 rate [76%] > HC rate [70%]).	-Simeprevir plus sofosbuvir for 12 weeks was efficacious and well tolerated in treatment-naive and treatment-experienced patients with HCV GT1 infection and cirrhosis. The primary objective of the study was met as simeprevir + sofosbuvir demonstrated

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						superiority in SVR12 rates (83%) compared with the HC (70%). In conclusion, simeprevir + sofosbuvir for 12 weeks was efficacious and well tolerated by treatment-naive and treatment-experienced patients with chronic HCV GT1 infection and cirrhosis.
Lawitz et al[188] 2015 **LOE-2**	Randomized, open-label phase 2 trial grazoprevir (100 mg daily) and elbasvir (50 mg daily) with or without ribavirin	N= 253 12 weeks and 18 weeks Follow up= 24 weeks	-Untreated adults aged 18 years or older with chronic infection with HCV genotype 1 who had compensated cirrhosis Additionally, enrolled PR-null responder patients	-The proportion of patients achieving HCV RNA less than 25 IU/mL at 12 weeks after end of treatment (SVR12)	-In cohort 1, SVR12 rates ranged from 90% (95% CI 74–98 [28/31] in arm B4) to 97% (95% CI 82–100 [28/29] in arm B5 and 95% CI 84–100 [31/32] in arm B6). One patient (arm B6) discontinued treatment early because of adverse events, one patient (arm B4) had virological breakthrough, and five patients (arms 4, 5, and 7) had virological relapse.	-High rates of efficacy were shown across all groups irrespective of the inclusion of ribavirin or extension of treatment duration from 12 to 18 weeks. Specifically, a regimen of 12 weeks of grazoprevir plus

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			(defined as patients who had a less than 2 log10 reduction in HCV RNA at treatment week 12 of a regimen of peginterferon and ribavirin, or who had a less than 1 log10 drop in HCV RNA at treatment week 4) with or without cirrhosis.		-In cohort 2, SVR12 rates ranged from 91% (95% CI 76–98 [30/33] in arm B9) to 100% (95% CI 89–100 [33/33]. -Sustained virological response rates for all treatment groups in both cohorts exceeded 90%, including in patients treated with the simplest, shortest regimen. -Within cohort 2, PR-null patients with cirrhosis achieved SVR12 rates of 92% (95% CI 74–99, 23/25) with	elbasvir without ribavirin showed efficacy of 97% in previously untreated patients with cirrhosis, 91% in null responder patients with or without cirrhosis, and 92% in null responder patients with cirrhosis. The rate of virological failure with grazoprevir plus elbasvir with or without ribavirin was low.
Leroy et al [197] 2016 **LOE-2**	Open-label, randomized phase IIIb study DCV-SOF-RBV 12 weeks VS DCV-SOF-RBV 18 weeks	N= 50 12/18 weeks w/ 24 week follow up	-Genotype 3-infected patients with advanced fibrosis or compensated cirrhosis	-The proportion of patients with SVR12, defined as a post-treatment virological response (HCV RNA <LLOQTD/TND) at week 12 after the treatment period	-SVR12 rates were similar for both 12 and 16 weeks of treatment with DCVSOF-RBV. By ITT analysis, SVR12 was 88% (21 of 24) in the 12-week treatment group and 92% (24 of 26) in the 16-week group, giving an overall rate in all treated patients of 90% (45 of 50). -All patients with advanced fibrosis achieved SVR12 (14 of 14;	-This study demonstrated a high level of efficacy and safety with DCV-SOF-RBV administered for 12 or 16 weeks to a challenging group of genotype 3-infected patients, most of whom had compensated

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					100%). Among patients with cirrhosis, 83% (15 of 18) achieved SVR12 in the 12-week group and 89% (16 of 18) in the 16-week group, for an overall rate of 86% (31 of 36). -In the subgroup of patients with cirrhosis and previous HCV treatment experience, SVR12 was 88% (14 of 16) in the 12-week group and 86% (12 of 14) in the 16-week group, giving an overall SVR rate of 87% (26 of 30).	cirrhosis and the rest advanced fibrosis, were treatment-experienced, and had high baseline HCV RNA levels. In this difficult-to-treat patient cohort, the overall SVR12 rate was 90%, and observed SVR12 did not differ with 12 versus 16 weeks of treatment.
Wyles et al[170] 2015 **LOE-2**	Randomized, open-label study Treatment-naïve were randomized 2:1 to receive: daclatasvir 60 mg QD and sofosbuvir 400 mg QD x 12 weeks Vs daclatasvir 60 mg QD and sofosbuvir 400 mg QD x 8W	N =203 (151 who were Hep C treatment naïve and 52 who had previously received treatment) Follow-up: 12 weeks after the end of therapy	-Adults with HCV genotypes 1-4 (83% genotype 1) who were coinfected with HIV	-Sustained virologic response at week 12 after the end of therapy among previously untreated patients with HCV genotype 1 who were treated for 12 weeks. - Key secondary efficacy end points were rates of sustained virologic	-For patients with genotype 1 infection, the rate of a sustained virologic response at post-treatment week 12 was 96.4% (95% CI, 89.8 to 99.2) among previously untreated patients who received 12 weeks of treatment (primary end point), 75.6% (95% CI, 59.7 to 87.6) among previously untreated patients who received 8 weeks of treatment, and 97.7% (95% CI, 88.0 to 99.9%) among previously treated patients who received 12 weeks of treatment.	-Among HIV–HCV coinfected patients who received 12 weeks of daclatasvir plus sofosbuvir, 97% had a sustained virologic response, regardless of whether they had received previous HCV treatment or a concomitant

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	Previously treated patients received: daclatasvir 60 mg QD and sofosbuvir 400 mg QD x 12 weeks			response at post-treatment week 12 among previously untreated patients with genotype 1 infection who were treated for 8 weeks and corresponding rates among previously treated patients who were treated for 12 weeks.	Among all patients, response rates were 97.0%, 76.0%, and 98.1%, respectively. - The rate of sustained virologic response after 8 weeks of treatment was lower overall and across subgroups, with the exception of patients with a baseline HCV RNA level of less than 2 million IU per milliliter (18 of 18 patients [100%]), as compared with patients with a level of 2 million IU per milliliter or more (20 of 32 patients [62%]). - The most common adverse events were fatigue, nausea, and headache. No patient discontinued treatment because of adverse events.	antiretroviral regimen, without disruption of HIV-1 virologic control. Daclatasvir and sofosbuvir were well tolerated.
Zeuzem et al[187] 2015 **LOE-1a**	Randomized, double-blind trial Randomized 3:1 to immediate or deferred therapy: grazoprevir 100 mg and elbasvir 50 mg QD x12 weeks	N=421 Follow-up: 12 weeks after the completion of therapy.	-Treatment naïve adults with chronic hepatitis C (genotypes 1, 4 and 6)	-Proportion of patients in the immediate treatment group achieving unquantifiable HCV RNA 12 weeks after treatment (SVR12) -Adverse events in both groups.	-Of the 316 patients in the immediate-treatment group, 299 (95% [CI, 92% to 97%]) achieved SVR12. SVR12 rates were 92% (144 of 157 [CI, 86% to 96%]) in patients with GT1 a infection, 99% (129 of 131 [CI, 95% to 100%]) in those with GT1 b, 100% (18 of 18 [CI, 82% to 100%]) in those with GT4, and 80% (8 of 10 [CI, 44% to	-Once daily grazoprevir-elbasvir achieved high SVR12 rates in treatment- naive cirrhotic and noncirrhotic patients with genotype 1, 4, or 6 infection.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					98%]) in those with GT6. SVR12 was achieved in 97% (68 of 70 [CI, 90% to 100%]) of cirrhotic patients and 94% (231 of 246 [CI, 90% to 97%]) of noncirrhotic. - Drug-related adverse events occurred in 114 (36.1%) and 41 (39.0%) patients in the active and placebo groups, respectively (difference, -2.9 percentage points). The most common adverse events were headache (17%), fatigue (16%), and nausea (9%).	
Zeuzem et al[167] 2016 **LOE-2**	Randomized, open-label study daclatasvir 30 mg QD, simeprevir 150 mg QD, and weight-based ribavirin x 12 weeks Vs daclatasvir 30 mg QD, simeprevir 150 mg QD x 12 weeks	N=168 Follow-up: 12 weeks after completion of therapy.	-Adults with chronic HCV genotype 1 infection who were treatment-naïve or prior null responders	- The proportion of patients with HCV RNA <LLOQ, detectable or undetectable, at posttreatment week 12 (SVR12). - Secondary efficacy endpoints included undetectable HCV RNA levels at week 4 and end of treatment.	- Among treatment-naive patients with genotype 1b, overall SVR12 rates were 84.9% with DCV + SMV and 74.5% with DCV + SMV + RBV. Among treatment-naive patients, SVR12 rates after 12 and 24 weeks of treatment, respectively, were 80.8% and 88.7% with DCV + SMV and 75.0% and 73.9% with DCV + SMV + RBV. Among prior null responders, SVR12 rates after 12 and 24 weeks of treatment, respectively, were 82.6% and 57.8%	-Among patients with genotype 1b, treatment for 12 or 24 weeks achieved combined SVR12 rates of 84.9% (DCV + SMV) and 74.5% (DCV + SMV + RBV) in treatment-naive patients and 69.6% (DCV + SMV) and 95.0% (DCV + SMV + RBV) in prior null responders. DCV + SMV was effective

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					with DCV + SMV and 100% and 88.9% with DCV + SMV + RBV. - Incidences of serious AEs and AEs leading to treatment discontinuation were low. AEs of any grade reported at a frequency P10% were asthenia, headache, nausea, pruritus, fatigue, nasopharyngitis, and dyspnea.	and well tolerated alone or in combination with RBV and with a 12-week treatment duration.
Feld et al[190] 2015 **LOE-1b**	Multicenter, randomized, double-blind, placebo-controlled study velpatasvir/ sofosbuvir 400mg/100mg QD Vs placebo	N=847 12 weeks	-Adult patients ≥18 years of age with HCV genotype 1, 2, 4, 5, or 6 who were untreated and previously treated, including those with compensated cirrhosis; patients who had previously received any nucleotide analogue HCV NS5B inhibitor or any NS5A inhibitor were not eligible	-The rate of sustained virologic response (SVR), defined as an HCV RNA <15IU/ml at 12 weeks after the end of treatment in patients who received ≥1 dose -Safety	-Of the 624 treated with velpatasvir/ sofosbuvir (V/S), 34% had genotype (G) 1a, 19% G1b, 17% G2, 19% G4, 6% G5, and 7% G6. -Overall, the rate of SVR among patients who received 12 weeks of V/S was 99%, which was significantly superior to the prespecified performance goal of 85% (p<0.001). None of the patients in the placebo group had SVR. -Rates of SVR were similar regardless of the HCV G: 98% G1a, 99% G1b, 100% G2, 100% G4, 97% G5, and 100% G6. -Of the V/S group, 2 (<1%) had	-Velpatasvir/ sofosbuvir use, given once daily, resulted in high rates of sustained virologic response in this population of previously treated and untreated patients infected with HCV.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					virologic failure. -Of the V/S group, 1 discontinued treatment due to an adverse event. 2% (N=15) of the V/S group had 19 serious adverse events. -Significant differences in the rates of adverse events were not different between treatment groups (78% V/S vs 77% placebo).	
Foster et al[191] 2015 **LOE-2**	Two Multicenter, randomized, phase 3, open-label studies velpatasvir/ sofosbuvir 400mg/100mg QD X12W OR sofosbuvir plus ribavirin (genotype 2, Astral-2 study) velpatasvir/ sofosbuvir 400mg/100mg QD X12W OR	N=266 (study 1) N=552 (study 2) 12 or 24 weeks	-Adults with HCV genotype 2 or 3 who had received previous treatment and those who had not received previous treatment, including patients with compensated cirrhosis	-Sustained virologic response (SVR) at 12 weeks after the end of therapy -Safety	*Astral-2 Trial:* -The rate of SVR at 12 weeks after treatment was 99% in the V/S group as compared with 94% with the sofosbuvir/ribavirin group. The S/V group met the primary endpoint with an SVR rate that was significantly superior to those in the sofosbuvir/ribavirin group (p=0.02). -There were no virologic failures in the S/V group. 5% (N=6) of the sofosbuvir/ribavirin group had a virologic relapse after the end of treatment, and 2 were lost to follow-up. *Astral-3 Trial:* -The rate of SVR at 12 weeks after	-In this population with HCV genotype 2 or 3 with or without previous treatment, including those with compensated cirrhosis, 12 weeks of velpatasvir/sofosbuvir resulted in SVR rates that were superior to sofosbuvir/ribavirin.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	sofosbuvir plus ribavirin X24W (genotype 3, Astral-3 study)				treatment was 95% among the S/V group as compared with 80% among the sofosbuvir/ribavirin X24W groups. The SVR rate of S/V was significantly superior to that of sofosbuvir/ ribavirin (p<0.001). -Of the S/V group, 11 (4%) had virologic failure after the end of treatment, and 2 were lost to follow-up. -In the group with V/S, the rate of SVR was 91% among those with cirrhosis as compared with 97% among those without cirrhosis. In the group with sofosbuvir/ribavirin, the rates of SVR of those with cirrhosis were 66% and those without cirrhosis were 87%. Safety: -In both trials, 1 patient discontinued treatment in the V/S group due to an adverse event. Serious adverse events were reported in 4 patients in trial 2 and in 6 patients in trial 3. -The most frequently reported	

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					adverse events included fatigue, headache, nausea, and insomnia.	
Curry et al[192] 2015 **LOE-2**	Multicenter, randomized, phase 3, open-label study velpatasvir/ sofosbuvir 100mg/400mg QD X12W Vs velpatasvir/ sofosbuvir 100mg/400mg QD PLUS ribavirin BID X12W Vs velpatasvir/ sofosbuvir 100mg/400mg QD X24W	N=267 12 or 24 weeks	-Adult subjects ≥18 years of age with chronic HCV infection of any genotype and decom-pensated cirrhosis, patients who had undergone liver transplantation were not eligible	-The sustained virologic response at 12 weeks after the end of therapy -Safety	Of the overall population, 78% had genotype (G) 1, 4% had G2, 15% had G3, 3% had G4, and <1% had G6. There were no patients with G5. -SVR rates were 83% in the V/S X12W group, 94% in the V/S plus ribavirin and 86% in the V/S X24W group. -All 3 groups met pre-specified primary endpoint, with rates of SVR that were significantly superior to the assumed spontaneous rate of HCV clearance at 12 weeks after treatment ($p<0.001$ for all 3 comparisons). -Post hoc analysis did not find any significant differences in rates of SVR among the 3 treatment groups. -There were a total of 22 with virologic failure, 12% (N=11/90) in the V/S X12W group, 3% (N=3/87)	-In this population with HCV infection and decompensated cirrhosis, treatment with velpatasvir/sofosbuvir with or without ribavirin for 12 weeks and velpatasvir/ sofosbuvir X24W resulted in high rates of SVR.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					in the V/S plus ribavirin group, and 9% (N=8/90) in the V/S X24W group. -Of the 22 who had virologic failure, 20 had relapse and 2 (both with G3) had virologic breakthrough. -There were 9 that discontinued treatment early due to an adverse event: 1 in the V/S X12W group, 4 in the V/S plus ribavirin group, and 4 in the V/S X24W group. -The most frequently reported adverse events included fatigue, nausea, and headache, although anemia, diarrhea, and insomnia were also common in patients who received V/S plus ribavirin.	
Ji D et all[195] 2016 **LOE-2**	Prospective observational cohort study	N=140	-Chinese adult subjects ≥18 years of age with treatment-experienced CHC GT1b including patients with cirrhosis	-Sustained virologic response at 24 weeks after end of therapy -Safety and cost effectiveness	-SVR 24 rates were significantly higher in the LDV-SOF and DVC-SOF than that of PR72 group ($p < 0.001$) -SVR 24 rates were 100% and 100% for groups LDV-SOF and DVC-SOF respectively. SVR 24 rates for PR72 group only 28.3%	-In Chinese patients with GT1b CHC, 12-week treatment with direct-acting antivirals without ribavirin achieved high SVR24 rates, cost effective, and less adverse events

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	daclatasvir/ sofosbuvir 60mg/400mg QD X12W Vs ledipasvir/ sofosbuvir 90mg/400mg QD X12W Vs peg-IFN-alpha 180 or 135 ug SQ weekly PLUS RBV 15/mg/kg/day X72W (PP72)	36 or 72 weeks			-All cirrhotic patients in DCV-SOF group (27/27, 100%) and LDV-SOF group 27/27, 100%) achieved SVR24, only 3 cirrhotic patients in PR72 achieved SVR24 (3/25, 12%) - Frequency of adverse events was 91.3% in the PR72 group, and 45.7% and 39.6% in DCV-SOF and LDV-SOF groups respectively ($p < 0.001$ for all comparisons) - There were 4 that discontinued treatment early due to adverse events in the PR72 group	
Sogni et al[196] 2016 **LOE-2**	Multicenter, hospital-based, prospective cohort study sofosbuvir/ daclatasvir +/- ribavirin X12 or 24W Or sofosbuvir/ ribavirin X12 or 24W Or sofosbuvir/ simeprevir+/- ribavirin X12 or 24W Or	N=189 12 or 24 weeks	-Patients enrolled in the French National Agency for Research on AIDS and Viral Hepatitis and started on all-oral Direct-acting Antiviral Agents (DAA) based regimen before May 1, 2015 and before February 1, 2015.	-The sustained virologic response at 12 weeks after the end of therapy -Safety	-SVR12 was reported in 176 (93.1%) patients. -SVR12 was similar in naïve (92.6%) compared with experienced. (93.3%) -In patients with Child-Pugh class B or C cirrhosis at DAA initiation, no statistically significant difference in SVR12 was observed compared with Child-Pugh class A. (81.3% vs 94.2%) -Of the overall population, 57% had genotype (G) 1, 3% had G2,	-In this observational cohort study of cirrhotic HIV/HCV-coinfected patients treated with DAA-based regimens, a high global SVR12 was seen in the real-life setting. Overall, the all-oral DAA regimes were well tolerated and associated with high virologic efficacy in cirrhotic

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	sofosbuvir/ ledipasvir+/- ribavirin X12 or 24W		-Patients participating in an ongoing clinical trial or receiving a combination including peg-IFN, or without sufficient follow-up results at end of treatment were excluded.		16% had G3, and 20% had G4. There were no patients with G5 or G6. -SVR12 was reported in 91.7%, 85.7%, 93.8%, and 97.4% for HCV Genotypes 1,2,3, and 4 respectively. -Treatment failure was reported in 13 patients: a virological relapse in 10 patients, virologic failure in 2 patients, and 1 patient died during treatment. -A virological relapse was reported in 5 patients previously treated with IFN/ Ribavirin, in 1 patient previously treated with peg-IFN/ribavirin/ telaprevir, and in 1 patient previously treated with another treatment. -A complication of cirrhosis occurred in 12 (6.6%) patients. Complications were reported in 8 patients: gynecomastia, renal insufficiency, mucositis, candidiasis, lipohypertrophy, and bronchitis.	HIV/HCV co-infected patients. **CHC Comments:** DAA regimen was at the discretion of the physician so dosing was not a controlled variable.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-Secondary effects attributed to the anti-HCV treatment were reported in 62 (33%) patients. Effects included fatigue, anemia, digestive disorders, skin disorders, mood disorders, insomnia, headache, cough, articular pain, muscular pain, and gynecomastia.	
Coilly et al[199] 2016 **LOE-2**	Prospective cohort multicenter sofosbuvir 400mg and daclatasvir 60mg QD X12 or 24W ±RBV 800mg QD X12 or 24W	N=137 12 or 24 weeks	-Received liver transplant for HCV infection, experienced an HCV recurrence and had been treated with a 2nd generation DAAs -Patients were ineligible if co-infected with HIV or diagnosed with fibrosing cholestatic hepatitis	-Sustained virological response 12 weeks after the end of treatment -Safety	-132/137 patients (96.4%) had an SVR at post treatment week 12 under the intention-to treat analysis -Cirrhosis patients had a SVR12 rate of 96% -2 patients experienced a virological failure, 1 patient was lost to follow-up, and 2 died between EOT and SVR12 -Adverse events affected 105 patients (77%), serious adverse effects affected 17.5% -Most adverse events were mild-moderate, most commonly anemia (56.3%)	- In Hepatitis C patients that had received liver transplants and treatment with sofosbuvir and daclatasvir, patients achieved high SVR12 and low rates of adverse reactions

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Welzel et al[201] 2016 **LOE-2**	International, prospective, observational study sofosbuvir 400mg PO once daily/ ribavirin 1000 or 1200mg once daily	N=321 12 or 16 weeks	-Adult patients with HCV GT2 >18 years enrolled in HCV-TARGET between December 8, 2013 and April 15, 2015. -Patients were excluded if they had undergone liver transplantation or previous treatment with a prior DAA.	-Sustained virological response 12 weeks after the end of treatment -Safety	-Analysis was done in the Evaluable Population (EP), patients who completed the regimen and have final treatment outcome available. Per Protocol Patients (PP), patients who completed the regimen and had virological outcomes available were also analyzed. -Overall, 283 of 321 patients (88.2%) achieved SVR12 in the EP while 283 of 307 (92.2%) in the PP population had a SVR12. -In the EP analysis, 283 (88.2%) and 38 (11.8%) of 321 patients received sofosbuvir and ribavirin for 12 or 16 weeks respectively. Among GT2-infected patients treated for 12 weeks, the overall SVR12 was 88.3%(250/283) and 86.8% (33/38) in those treated for 16 weeks. -In patients without cirrhosis, SVR12 was 91% (201/221) in patients who received 12 weeks of sofosbuvir and ribavirin and 92.9% (13/14) among patients treated for 16 weeks. SVR12 rates in	-This large, international observational study demonstrated a high efficacy of sofosbuvir and ribavirin. Overall SVR12 rate was 88.2% (283/321). Both treatment durations of sofosbuvir in combination with weight-based ribavirin in this clinical practice setting were well tolerated. **CHC Comments**: Selection of the appropriate ribavirin dose and determination of the treatment duration were the physician's choice. Did not report statistical significance of

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					patients with cirrhosis treated for 12 or 16 weeks were 79%(49/62) and 83,3% (20/24%), respectively. -The PP population included 271 (88.3%) and 36 (11.7%) treated for 12 and 16 weeks respectively. Among GT-2 infected patients treated for 12 weeks, the overall SVR12 rate was 92.3% (250/271) and 91.7% (33/36) in those treated for 16 weeks. -In patients without cirrhosis, SVR12 was 93.9% (201/214) in patients who received 12 weeks of sofosbuvir and ribavirin and 100% (13/13) among patients treated for 16 weeks. SVR12 rates in patients with cirrhosis treated for 12 or 16 weeks were 86% (49/57) and 87% (20/23), respectively. -Only 24 discontinued early for: AEs 10(2.8%), lost to on-treatment follow-up 9 (2.5%), non-compliance 3(1%), and 2 (<1%) due to other reasons Safety: -Only 10 of 361 (2.8%) patients	primary outcome.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					discontinued treatment prematurely due to an AE. Of those, eight patients had liver cirrhosis. -AE's were reported in 268/321 (83.5%) patients of the EP. -Six patients (1.9%), all with cirrhosis, who started treatment with SOF and RBV died. Reported cause of death was multiorgan failure in three patients, cardiac arrest in two patients, and hepatic encephalopathy in one patient.	
Backus et al[202] 2016 **LOE- 2**	Observational intent-to-treat cohort ledipasvir/ sofosbuvir (LDV/SOF) VS LDV/SOF PLUS ribavirin Vs ombitasvir/ paritaprevir/ ritonavir/ dasabuvir (OPRD) Vs OPRD PLUS ribavirin	N=6961 8 or 12 weeks	-Adult subjects (Veterans) >/ 18 years of age with genotype 1 HCV, who initiated 8 or 12 weeks LDV/SOF ±RBV or 12 weeks of OPrD ± RBV, patients changed regimens without treatment	-Sustained virologic response (SVR) at the 10 weeks time point	-SVR was available for 94.0% (n=6542) of patients. Among 4170 LDV/SOF patients, 91.4% achieved SVR; among 1220 LDV/SOF + RBV patients 90.0% achieved SVR; among 283 OPrD patients 95.1% achieved SVR and among 869 OPrD + RBV patients, 85.8% achieved SVR. -Impact of treatment of duration among patients who received LDV/SOF, the SVR rate in those who received 8 weeks was 91.7% and 94.6% for those who received	-In the comparative effectiveness analysis of LDV/SOF ± RBV VS OPrD ± RBV in genotype 1 HCV infected veterans treated in routine medical practice, high SVR rates were achieved overall (86-95%).

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			interruption were not eligible.		12 weeks. Patients completing 12 weeks of LDV/SOF + RBV had an SVR rate of 92.2%, patients completing 12 weeks of OPrD + RBV had a SVR rate of 95.5%.	
Ioannou et al[203] 2016 **LOE-2**	Retrospective cohort sofosbuvir, ledipasvir/ sofosbuvir, and paritaprevir/ ritonavir/ ombitasvir and dasabuvir (PrOD)	N=17,487 8-week, 12-week, or 24-weeks	-Patients infected with hepatitis C genotypes 1, 2, 3, or 4 using Sofosbuvir, ledipasvir/ sofosbuvir, and paritaprevir/ ritonavir/ ombitasvir and dasabuvir (PrOD)	-Sustained viral response 12 (SVR12) weeks after the end of treatment	-Patients in HCV genotype 1 had an SVR12 for 92.8%, no significant difference between ledipasvir/ sofosbuvir and PrOD treatment groups -Patients in HCV genotype 2 had an SVR12 for 86.2% treated with sofosbuvir and ribavirin -Patients in HCV genotype 3 had an SVR12 of 74.8%; 77.9% in patients treated with ledipasvir/ sofosbuvir with ribavirin, 87% in patients treated with sofosbuvir and pegylated interferon with ribavirin, and 70.6% in patients treated with sofosbuvir - Patients in HCV genotype 4 had an SVR12 89.6%	-In real world clinical practice sofosbuvir, ledipasvir/ sofosbuvir, and paritaprevir/ ritonavir/ ombitasvir and dasabuvir (PrOD) treatment regimens can achieve high SVR rates for patients infected with hepatitis C genotypes 1, 2,3, or 4.
Mizokami et al[204] **LOE-2**	Resistance analysis of two open label, randomized, phase 3 trial	N= 341 of GT1 trial N= 153 of GT2 trial	-Subjects 20 years or older with body weight ≥ 40kg and HCV and	-Evaluated the effect of baseline HCV NS5A and NS5B resistance-associated variants (RAVs) on treatment	-A total of 22.3% (76 of 341) of GT1 patients were identified as having at least one baseline NS5A RAV. Of these 76 patients 98.7% (75/76) achieved SVR12 compared	-Treatment with all-oral, interferon-free combination of LDV/SOF+/-RBV in GT1 patients and

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	GT1 patients: ledipasvir/ sofosbuvir +/- ribavirin 90/400mg once daily +/- weight-based dosing per package insert once daily GT2 patients: sofosbuvir/ ribavirin 400/ weight-based dosing per package insert once daily	12 weeks	RNA ≥ 10^5 IU/mL at screening were included. -Current or history of any clinically significant illness (besides HCV), pregnant or nursing female or male with pregnant partner, chronic liver disease of non-HCV etiology, or infection with HBV or HIV patients were all excluded from the study.	outcome and characterized variants at virologic failure.	with 99.2% (263/265) without baseline RAVs. -The GT1 study included 11 GT1a (3.2%) patients and 330 GT1b (96.8%) patients. Among the GT1 patients, 48.7% were treatment naïve, 51.3% were treatment experienced and 22.3% had cirrhosis. -A total of 60.7% (93 of 153) of GT2 patients were identified as having a NS5B sequence. All patients with NS5B RAVS at baseline achieved SVR12 (100%) -The overall HCV genotype distribution for the GT2 study was 92 GT2a (60.1%) and 61 GT2b (39.9%). Among the GT2 patients, 58.8% were treatment naïve, 41.2% were treatment experienced and 11.1% had cirrhosis.	SOF +RBV in GT2 patients resulted in high rates of SVR in both treatment naïve and previously treated patients. The treatments demonstrated a high barrier to resistance. NS5A and NS5B RAVs did not impact treatment. **CHC Comments**: Study performed only in Japanese patients, which may limit external validity.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Chamorro-de-Vega[206] 2016 **LOE-2**	Single-center, prospective, observational study ombitasvir/ paritaprevir/ ritonavir and dasabuvir VS ombitasvir/ paritaprevir/ ritonavir and dasabuvir PLUS ribavirin	N=121 12 weeks	-Adult subjects ≥ 18 years of age with genotype 1 infection, patients with HIV coinfection, liver transplantation and previous treatment with any other interferon-free combination were not eligible	-The percentage of patients who achieved SVR12. -The percentage of patients who achieved SVR12 according to different subgroups: use or nonuse of ribavirin, cirrhotic or not cirrhotic, genotype 1a or 1b, and naïve or pretreated. -Safety	-The overall SVR12 rate was 95.9% in an intent-to-treat analysis. HCV patients who received ribavirin had similar response rates of 95.3% as not receiving ribavirin at 97.1%. -Among patients with cirrhosis, 93.8% achieved SVR12 and noncirrhotic patients have a 100% SVR12 rate. -Adverse events occurred in 91.7% of the study patients. There was no premature discontinuation due to adverse events. The most common adverse events were anemia, fatigue, pruritus, insomnia, headache, irritability, dry skin, and decreased appetite.	-The results corroborated high effectiveness in cirrhotic and noncirrhotic populations, (93.8% and 100% of SVR12, respectively), with an overall SVR12 rate of 95.9%. -The combination of OBV/PTV/r + DSV with or without ribavirin for 12 weeks confirms a high rate of SVR12 in the treatment of HCV GT1. -Incidence of adverse events were high, although this did not lead to premature drug discontinuation. **CHC Comments:** absence of randomization

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Dore et al[207] 2016 **LOE- 2**	Two Phase IIIb, randomized, open label studies ombitasvir/ paritaprevir/ ritonavir (OBV/PTV/r) and dasabuvir (DSV) PLUS ribavirin Vs telaprevir (TPV)/and pegylated interferon (PegIFN)/ribavirin ombitasvir (OBV)/ paritaprevir (PTV)/ritonavir and dasabuvir PLUS ribavirin Vs ombitasvir/ paritaprevir/ ritonavir and dasabuvir Vs telaprevir and pegylated interferon/ ribavirin	N=459 12 weeks of treatment Follow up: 48 weeks post-treatment	-Adults age 18-65 years of age with HCV genotype 1 and HCV RNA. 10,000 IU/ml patients with positive hepatitis B surface antigen or anti-HIV antibody screen, and current or past evidence of cirrhosis were not eligible.	-Percentage of patients with SVR12 (HCV RNA < lower limit of quantitation (LLOQ)) -Secondary endpoints included mean change from baseline to final treatment visit in Physical Component summary (PCS) and Mental Component summary (MCS).	*Malachite-I Trial:* -Among HCV GT1a-infected patients, 97% receiving OBV/PTV/r + DSV + RBV and 82% receiving TPV + PegIFN/RBV achieved SVR12. -Among HCV GT1b-infected patients, 98% receiving OBV/PTV/r + DSV and 78% receiving TPV + PegIFN/RBV achieved SVR12. *Malachit-II Trial* -99% of patients receiving OBV/PTV/r + DSV+RBV achieved SVR12. 66% of patients receiving TPV+PegIFN/RBV achieved SVR12. -SVR12 rates were 100% and 57% in prior null responders receiving OBV/PTV/r + DSV+RBV and TPV+ PegIFN/RBV, respectively. -Across the two studies, 46% and 58% of patients receiving OBV/PTV/r + DSV ±RBV showed numerical improvement over baseline at final treatment visit in MCS and PCS, respectively; 27% and 22% of patients receiving	-The SVR12 rate was numerically higher with OBV/PTV/r + DSV ± RBV than TPV + PegIFN/RBV regardless of subgenotype or prior treatment status. -Mean changes in SF-36v2 MCS and PCS scores from baseline were numerically and significantly different between OBV/PTV/r + DSV ± RBV and TPV + PegIFN/RBV throughout the treatment period, with the difference indicating better mental and physical health in patients receiving OBV/PTV/r + DSV ±RBV.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					TPV+ PegIFN/RBV showed numerical improvement in MCS and PCS.	**CHC Comments:** Internal study validity limited due to lack of blinding.
Lawitz et al[208] 2016 **LOE-2**	Multicenter, open label, single arm, Phase 3 study simeprevir and sofosbuvir Vs historical control from that used peginterferon and ribavirin plus either simeprevir or sofosbuvir	N=103 intent to treat population 12-week study duration Data analysis duration: April 16, 2014 – January 16, 2015	-Eligible patients were 18-70 years and had HCV genotype (GT) 1, plasma HCV RNA concentration >10,000 IU/mL, and presence of cirrhosis. They had to have undergone hepatic imaging <6 months before screening with no suspicion of hepatocellular carcinoma. Patients were excluded if they had evidence of hepatic decom-pensation, any liver disease of non-HCV etiology, and	-Demonstrate superiority of simeprevir/ sofosbuvir for 12 weeks versus a historical control with respect to the proportion of patients achieving a sustained virologic response at 12 weeks (SVR12). -Proportion of patients achieving SVR 4 and 24 weeks after end of trial; proportion of patients with on-treatment virologic response, rates of on-treatment failure, incidence of viral relapse. -Safety	- SVR12 rate for simeprevir/sofosbuvir was superior to the historical control (76% vs 70%), respectively. - HCV RNA <25 IU/mL undetectable at week 4 in 83% of patients, where 86% of those achieved SVR12. On-treatment failure occurred in 3% of patients, 2% experienced viral breakthrough at weeks 4 and 8, and 13% experienced viral relapse. -The most common AEs reported were headache (20%), fatigue (20%), and nausea (11%); these effects were graded at 1 or 2, were transient, and did not lead to permanent treatment discontinuation; 64% of patients reported grade 1 or 2 AEs.	- Simeprevir/sofosbuvir for 12 weeks was efficacious and well tolerated by treatment-naïve and treatment-experienced patients with chronic HCV GT1 infection and cirrhosis. **CHC Comments:** Limitations of this study included the lack of a comparator arm, that it was open-label, and some subgroups had a small n which limited the conclusions that could be drawn by this trial.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			infection/co-infection with HCV non-GT1, hepatitis B, or HIV.			
Watanabe T et al[209] 2016 **LOE-2**	Prospective, multicenter study simeprevir 100mg for 12 weeks plus Peg-IFN/RBV for 24 weeks	N=176 Up to 36 weeks. Therapy was discontinued at week 12 if patient had <100 IU/mL reduction in HCV RNA or an increase in HCV RNA of more than 100 IU/mL.	-Patients had a median age of 62 years, had HCV GT1, and plasma HCV RNA of 100,000 IU/mL. They were at 10 hospitals throughout Japan. Exclusion criteria: Liver cirrhosis or hepatic failure, liver disease of non-HCV etiology, co-infection with non-GT1 HCV, hepatitis B, or HIV, organ transplant, or history of hepatocellular carcinoma	-The proportion of patients with an undetectable HCV RNA at the end of treatment and 12 weeks after the last treatment. -Proportion of patients with undetectable HCV RNA at EOT, undetectable HCV-RNA at EOT and 4 weeks after last treatment, viral breakthrough	- 81.8% of patients had an undetectable HCV RNA level at the EOT and 12 weeks after the last treatment. - 96.4% of all patients had an undetectable level at EOT and 88.6% of all patients had a SVR4. Treatment was discontinued in 20 patients (11.3%); 3 were due to viral breakthrough and 2 were due to virologic stopping criteria. -Patients who were <60 had a SVR12 of 79.7% when compared to all other 60 and older whose SVR12 was 83.2%. Patients who were <70 had a SVR12 of 83.8% when compared to all other 70 years and older it was 62.5%. In both breakdowns, those aged greater than or equal to 60 or 70 years old had more treatment discontinuation compared to their younger counterparts.	-Simeprevir with Peg-IFN and ribavirin have good efficacy and tolerability even in elderly patients, but viral relapse after completing treatment was high in patients aged over 70 years. Patients <70 years and those discontinuing previous DAAs would be suitable for this treatment. **CHC Comments:** This study paid particular focus to elderly patients with HCV.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			within 5 years of study entry.			
Coilly et al[210] 2016 **LOE-2**	Multicentre, prospective cohort observational study sofosbuvir (SOF) and daclatasvir (DCV) 400-60mg with or without ribavirin (RBV)	N= 559 Planned for 12 or 24 weeks, but investigators could extend that period if was clinically necessary	-Patients were in either a French or Belgian facility, and the majority are GT1. Received a liver transplant for HCV infection, experience an HCV recurrence whatever the stage of fibrosis, and been treated with second-generation DAAs	-Proportion of patients who achieved undetected HCV RNA levels or an SVR at week 12 after treatment discontinuation. -Virological failures, viral breakthroughs and relapse rates, and liver function improvement.	-132 out of 137 (96.4%) had an SVR at post-treatment week 12. The SVR12 rate reached 98.5% (132/134). -Two patients experienced virological failure. Among potential candidates for a re-transplantation with a MELD score at baseline over 15, 65% improved between 1 and 10 points. Ascites disappeared in 3 out of 5 of the patients with mild-moderate ascites at baseline. - Overall, the regimen was safe and well-tolerated	-It was found that the combination of DCV and SOF with or without RBV administered for 12 or 24 weeks enabled an SVR12 rate of 96% among liver transplant patients. **CHC Comments:** One limitation to the study was the difficulty of comparing efficacy per the duration of treatment or the use of RBV.
Sogni et al[212] 2016 **LOE-2**	Prospective, multicenter hospital-based cohort of HIV/HCV co-infected patients Had to be on an all-oral-DAA-based regimen	N= 189 Had to start 12 weeks therapy before May 1, 2015 and 24-	-Patient were predominantly male, treated with combination antiretroviral therapy, and HIV RNA was undetectable in 87% of them.	-The success of treatment which was defined as a negative HCV RNA results below the limit of detection at SVR12. -Viral breakthrough, virologic failure, adverse events	-176 patients (93.1%) achieved SVR12. SVR12 was similar in naïve patients at 92.6% compared to experienced patients at 93.3%. SVR12 was reported in 91.7%, 85.7%, 93.8%, and 97.4% for HCV genotypes 1, 2, 3, and 4, respectively. -Treatment failure was reported in	-In this real-life observational cohort, new all-oral DAA regimens were well tolerated and are associated with high virologic efficacy in HIV/HCV co-infected cirrhotic patients.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
		week therapy before February 1, 2015. Study lasted until 12 weeks after treatment ended.	Median CD4 counts was 489. HCV treatment-naïve patients represented 29% of the population.		13 patients (10 relapsed, 2 had virologic failure, and 1 died during treatment). No viral breakthroughs were reported. -A complication of cirrhosis occurred in 12 patients and secondary effects like fatigue, anemia, digestive disorders, and skin disorders occurred as secondary effects of treatment.	**CHC Comments:** Not a randomized trial and a small sample size causing a lack of power to identify independent risk factors.
Welzel et al[213] 2016 **LOE-2**	Prospective, longitudinal, observational cohort study sofosbuvir (SOF) 400mg QD and weight-based ribavirin (RBV) either 1000mg/day (≤75kg) or 1200mg/day (>75kg)	N= 321 Duration of treatment: 12 or 16 weeks	-Adult patients who initiated HCV treatment with DAA agents. They specifically wanted to look at those with a GT2. Pts were excluded if they had undergone liver transplantation or had previously been treated with a prior DAA.	-SVR12 defined as HCV RNA below the lower limit of quantification or undetectable at least 64 days after treatment was discontinued.	-88.2% achieved a SVR12 in the evaluable population (EP) which is defined as the group of patients who completed either 12- or 16-week regimens and have the final treatment outcome available, and it includes those who were lost to follow-up. 92.2% achieved a SVR12 in the per protocol population which is defined as the group who completed 12 or 16 weeks and have virological outcomes available. -Among GT2 patients in the EP SVR12 was 88.3% and 86.8%, respectively 12- and 16-week treatments. In the PP group SVR12 was 92.3% and 91.7%, respectively 12- and 16-week treatments.	-The all-oral combination of SOF and RBV was safe and effective for treatment of HCV GT2. Larger trials are needed to determine the benefit of extended treatment durations of SOF and RBV for those with liver cirrhosis. **CHC Comments:** Limitations included small sample size and is a cohort not a randomized trial.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-In patients with cirrhosis treated for 12 weeks, 93.9% in the PP population reached SVR12, and 100% of patients who had cirrhosis and were treated for 16 weeks in the PP reached SVR12. -38 patients did not achieve SVR12 and the most common reason was for virological failure was relapse.	
Chamorro-de-Vega et al[214] 2016 **LOE-2**	Single-center, prospective, observational cohort ombitasvir/ paritaprevir/ ritonavir and dasabuvir (OBV/PTV/r+ DSV) 25/150/100mg and DSV 250mg BID	N= 121 12 weeks and follow-up for 12 weeks	-Patients were eligible for enrollment if they were 18 years or older, had GT1, and it didn't matter if they have previous treatment of chronic HCV infection or the fibrosis stage. Patients with HIV co-infection, liver transplantation, or previous	-The percentage of patients who achieved SVR12 -Percentage of patients who achieved SVR12 per different subgroups: use or nonuse of ribavirin, cirrhotic or not cirrhotic, genotype 1a or 1b, and naïve or pretreated.	-The overall SVR12 rate was 95.9% in an ITT analysis. Response rates were similar for those HCV patients who received ribavirin and didn't receive ribavirin, 95.3% and 97.1% respectively. 5 patients failed to reach SVR12. -Among those with cirrhosis and without cirrhosis, 93.8% and 100% achieved SVR12.	-In summary, the combination of OBV/PTV/r+DSV with or without ribavirin for 12 weeks confirms a high rate of SVR12 in the treatment of HCV genotype 1 infection under routine clinical practice. **CHC Comments:** Limitations included: small sample sizes, especially in the

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			treatment with any other interferon-free combination were excluded.			sub-groups examined and not randomized.
Sperl et al[215] 2016 **LOE-2**	Randomized, multi-site, open label phase 3 trial elbasvir/ grazoprevir 50/100mg (EBR/GZR) Vs sofosbuvir 400mg and Peg-IFN + ribavirin dosed based on weight (SOF/PR)	N= 257 were randomized (129 to EBR/GZR and 128 to SOF/PR) The first patient started treatment on March 22, 2015 and the final patient completed 12 weeks follow-up on November 26, 2015.	-HCV GT 1, 4, or 6 with a baseline viral load > 10,000 IU/mL patients in Europe and Turkey.	-Comparison of SVR12 after the end of all study therapy which was defined as an RNA load <15 IU/mL in patients receiving EBR/GZR compared with SOF/PR.	-The SVR12 rates were 99.2% and 90.5% in the EBR/GZR and SOF/PR groups, respectively. 1 patient in the EBR/GZR group and 12 patients in the SOF/PR group did not achieve SVR12. -Both noninferiority and superiority of EBR/GZR vs. SOF/PR was established with the lower bound of the 1-sided 1-sample exact test was greater than -10% and was greater than zero.	-In summary, this study suggests that a once daily fixed-dose combination of EBR/GZR for 12 weeks has a superior efficacy and safety profile in the treatment of patients with HCV GT1, or 4 infection compared with SOF/PR. **CHC Comments:** The results for GT4 should be interpreted with caution due to the small number in this current study. The overall majority of patients had genotype 1.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Flisiak et al[216] 2016 **LOE-2**	Multicentre, open-label, investigator-initiated cohort study ombitasvir/ paritaprevir/ ritonavir ± dasabuvir ± ribavirin (OBV/PTV/r ±DSV ± RBV 25mg/150mg/ 100mg ± 500mg/day ± 1000 or 1200mg per weight	N= 209 12 weeks in most, but up to 24 weeks if liver cirrhosis infected with HCV GT1a,1, or 4, and in all post-OLTx patients.	-Adults with HCV GT1 or 4, previously treated or treatment-naïve, with liver cirrhosis or post-orthotopic liver transplantation (OLTx). Pts with noncirrhotic livers were also included if an intolerance to PEG-IFN was documented.	-The proportion of patients with SVR12. The detection level was either <18 IU/mL or <15 IU/mL depending on the study center.	-Among the 202 participants who completed the scheduled therapy, only 2 did not achieve SVR12. SVR12 was achieved in 100%, 98.9%, and 100% of patients with GT1a, 1b, and 4 respectively. SVR12 was achieved in 98.3% of those with cirrhosis. Overall, 99% of patients achieved SVR12.	-In summary, OBV/PTV/r ± DSV ± RBV therapy proved highly effective in patients with chronic HCV infection including individuals with advanced liver disease, a history of non-response to PEG-IFN based regimens, or post-OLTx. With its good virologic outcomes and low risk of serious adverse event, this regimen is a good choice for those with chronic HCV GT1 infection.
Reddy et al[221] 2017 **LOE-2**	Longitudinal, observational cohort study using HCV-TARGET, an international consortium of academic & community medical centers	N= 220	-Patients were 18 years and older and had to be treated with an all-oral DAA regimen according to standard care.	-To evaluate SVR12 Safety	-SVR in GT1 was higher when treated with sofosbuvir/simeprevir than those treated with sofosbuvir/RBV, 74% vs. 54% respectively. SVR rates were similar among treatment-naïve and treatment-experienced GT1 patients in the regimens with	-SOF-based HCV therapy in GT1 and GT2 patients with advanced liver disease presents a good option. Long-term follow-up is needed to address

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	sofosbuvir/ ribavirin (SOF+RBV) Vs sofosbuvir/ simeprevir Vs sofosbuvir/ simeprevir/ ribavirin	Enrolled patients who started treatment between December 2013 and October 2014	Patients were required to have a MELD score ≥10, have no prior liver transplant history, and have an available treatment outcome.		SOF/simeprevir with or without RBV. In genotype 2 patients, SVR12 was achieved in 72% of patients with SOF/RBV, whereas only 35% achieved SVR12 in those with GT3.	the benefits of eradicating HCV infection in those with advanced liver disease.
Fox et al[223] 2016 **LOE-2**	Retrospective cohort from the Veterans Health Administration simeprevir/ sofosbuvir ± ribavirin (SIM/SOF ±RBV) OR ledipasvir/ sofosbuvir ± ribavirin (LDV/SOF ± RBV) OR ombitasvir/ paritaprevir/ ritonavir/ dasabuvir (3D) ± RBV	N= 11,464 Treatment had to be stopped by July 1, 2015, followed patients for 12 weeks after completing treatment and on average treatment last 12 weeks.	-All HCV infected patients nationwide (US) were included if they initiated treatment with any of the three study regimens and stopped treatment prior to July 1, 2015 If a patient was initiated on more than one DAA on the same date, they were excluded.	-To compare sustained virologic response rates achieved 12 weeks post-treatment in patients treated with three different regimens	-The unadjusted SVR12 rates were 85.3% for SIM/SOF/RBV, 89.3% for LDV/SOF/RBV, and 84.2% for 3D/RBV. The SVR12 rates for patients treated without ribavirin were 82.8%, 92.4%, and 90.2%, respectively. SVR12 rates were lower for patients with cirrhosis, decompensated cirrhosis and HCC.	-Among genotype 1 patients, all three study regimens worked well in real world practice, achieving SVR12 rates comparable to those observed in pre-approval randomized clinical trials. The LDV/SOF/RBV regimen appears to have performed best. It is also of note that both SIM/SOF and 3D are now contraindicated for patients with

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						decompensated cirrhosis.
Calleja et al[228] 2017 **LOE-2**	Multicenter, retrospective, non-interventional, Spanish cohort study ombitasvir/ paritaprevir/ ritonavir plus dasabuvir (OMV/PTV/r/ DSV) Or ledipasvir/ sofosbuvir (LDV/SOF)	N= 3325 Follow up ranged from 24 to 36 weeks depending on treatment duration.	-Patients were chronically infected with HCV GT1a or 1b in 35 Spanish Centers.	-Outcomes included assessing virologic response and this was looked at Week 4 for EOT, SVR4, and SVR12.	-(OMV/PTV/r/DSV): SVR12 achieved was 96.8%, and there was no significant difference in SVR12 per genotype or fibrosis stage. Of those patients with available data, HCV RNA was undetectable at treatment week 4 in 93.1%, at EOT in 98%, and 98% achieved SVR4. -LDV/SOF: 95.8% of patients achieved SVR12, and there was no significant difference per genotype or fibrosis stage. In all patients with available data, 81.9% has undetectable viral load at week 4, 98.4% and 96.2% has response at EOT and SVR4, respectively.	-In summary, both OMV/PTV/r/DSV and LDV/SOF yielded similar or higher rates of SVR12 in the real-world setting compared with randomized control trials. **CHC Comments:** These two regimens cannot be directly compared, so the results were presented as two separate groups.
Alam et al[234] 2017 **LOE-2**	Phase 4, prospective, observational, study (SONET) simeprevir-containing HCV treatment regimen as per routine clinical practice	N=315 patients February 2014 through November 2015	-Patients ≥18 years old with chronic genotype 1 HCV infection	-Proportion of patients who achieved sustained virologic response 12 weeks after the treatment (SVR12). Secondary outcomes:	-SVR12 was achieved by 81.2% (255 of 314) of ITT patients (analysis excluded 1 patient who completed the study but was missing SVR12 data); 2 had viral breakthrough and 18 had viral relapse.	-Simeprevir-based treatment was effective and well tolerated in this cohort.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
				proportion of patients who had sustained virologic response 4 weeks after the end of treatment (SVR4), rapid virologic responses (RVR), viral breakthrough, and viral relapse	-SVR12 was achieved by 92.4% (255 of 276) of patients in the modified ITT (mITT) population, which excluded patients who discontinued treatment for nonvirologic reasons before the SVR12 time point or were missing SVR12 assessment data. -SVR4 was achieved by 254 of 313 (81.2%) of patients. RVR was achieved by 169 of 264 (64%) of patients. 2 patients had viral breakthrough and 18 patients had viral relapse.	
Asselah et al[235] 2016 **LOE-2**	Multicentre, randomized, open-label phase 3 trial (AGATE-I) 25mg ombitasvir/ 150mg paritaprevir/ 100mg ritonavir once daily, with weight-based ribavirin BID for either 12 or 16 weeks	N=120 patients 12 or 16 weeks	-Patients ≥18 years old, treatment-naïve and interferon or pegylated interferon and ribavirin treatment-experienced patients with HCV genotype 4 infection and compensated cirrhosis	-Proportion of patients with a sustained virological response at post-treatment week 12 (SVR12)	-SVR12 was achieved in 57 (97%; 97.5% CI 86.7 to 99.2) of 59 patients in the 12-week group and 60 (98%; CI 89.6 to 99.8) of 61 in the 16-week group. -For both treatment groups, superiority to the predefined threshold was shown because the lower bounds of the Cis for the proportion of patients with SVR12 were higher than 67%.	-Authors concluded that the study showed superiority of 12 weeks and 16 weeks of ombitasvir/paritaprevir/ ritonavir plus weight-based ribavirin to the historical control (pegylated interferon and ribavirin). The also they stated they saw no benefit of

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						16-week treatment groups for patients with HCV genotype 4 infection and compensated cirrhosis.
Bourliere et al[236] 2017 **LOE-2**	Two phase 3 (POLARIS-1 and POLARIS-4) POLARIS-1: Sofosbuvir/ velpatasvir/ voxilaprevir or placebo once daily for 12 weeks POLARIS-4: sofosbuvir/ velpatasvir/ voxilaprevir or sofosbuvir/ velpatasvir for 12 weeks	POLARIS-1: November 2015 through May 2016; 300 patients; 12 weeks POLARIS-4: January through May 2016; 314 patients; 12 weeks	POLARIS-1: patients with HCV genotype 1 who had previously received a regimen containing an NS5A inhibitor POLARIS-4: patients with HCV genotype 1, 2, or 4 who previously received a DAA regimen but not an NS5A inhibitor	-Sustained virologic response 12 weeks (SVR12) after the end of treatment	-POLARIS-1: SVR rate was 96% with sofosbuvir/ velpatasvir/ voxilaprevir (95% CI 93 to 98; p<0.001) vs. 0% with placebo. All patients with an SVR at week 12 had an SVR at week 24. -POLARIS-4: SVR rate was 98% (95% CI 95 to 99; p<0.001) with sofosbuivr/ velpatasvir/ voxilaprevir vs. 90% (95% CI 84 to 94; p=0.09) with sofobuvir/ velpatasvir. All patients with an SVR at week 12 had an SVR at week 24. -One patient in the sofosbuvir/ velpatasvir/ voxilaprevir group had a virologic relapse. In the sofosbuvir/ velpatasvir group, 14 patients had a relapse and 1 had virologic breakthrough.	-Daily treatment with sofosbuvir/ velpatasvir/ voxilaprevir for 12 weeks is effective for the treatment of HCV of any genotype for patients with or without cirrhosis, who did not have an SVR after treatment with a DAA-based regimen.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Gane et al[237] 2017 **LOE-2**	Multicenter, open-label, phase 2 study sofosbuvir/ velpatasvir (400mg/100mg) plus weight-adjusted ribavirin	N=69 24 weeks	-Patients ≥18 years old with documented HCV infection who did not achieve SVR after prior treatment with DAA regimens	-Proportion of patients achieving SVR12	-63 of 69 patients (91%; 95% CI 82 to 97%) achieved SVR12. Four patients did not achieve SVR12 due to relapse. Two patients had on-treatment virologic failure. -Adverse events reported included fatigue, nausea, headache, insomnia, and rash.	-Retreatment of patients who previously failed DAA-based therapies with sofosbuvir-velpatasvir plus ribavirin for 24 weeks was well tolerated and effective.
Gane et al[238] 2016 **LOE-2**	Multicenter, open-label, 2-cohort, phase 2 study sofosbuvir/ velpatasvir (400mg/100mg) plus GS-9857 (100mg) daily GS-9857: voxilaprevir	N=128 6-12 weeks	-Patients ≥18 years old with documented HCV infection with genotypes 2, 3, 4, 5, or 6. Cohort 1: Treatment-naïve patients without cirrhosis received 6 weeks of treatment vs. 8 weeks of treatment with cirrhosis. Cohort 2:	-Proportion of patients achieving SVR12 Secondary: proportion of patients with virologic failure	-Cohort 1: SVR12 rates were 88% (29 of 33; 95% CI 72 to 97%) in patients without cirrhosis receiving 6 weeks of treatment and 93% (28 of 30); 95% CI 78 to 99%) in patient with cirrhosis receiving 8 weeks of treatment -Cohort 2: SVR12 rates were 100% (36 of 36; 95% CI 90 to 100%) in patients without cirrhosis and 97% (28 of 29; 95% CI 82 to 100%) in patients with cirrhosis after 12 weeks of treatment -All 7 patients who did not achieve SVR12 had virologic relapse.	-Sofosbuvir/ velpatasvir plus GS-9857 was safe and effective for patients with HCV genotype 2, 3, 4, or 6 infections with or without compensated cirrhosis. 8-week treatment duration for naïve patients or 12 weeks in treatment-experienced patients was effective.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			Treatment experienced patients and all received 12 weeks of treatment.			
Gane et al[239] 2016 **LOE-2**	Multicenter, open-label, phase 2 study sofosbuvir/ velpatasvir (400mg/100mg) plus GS-9857 (100mg) daily of 4, 6, and 8 weeks	N=161	-Patients ≥18 years old with documented HCV infection genotype 1 or 3 who were treatment naïve or previously treated patients 1 group of treatment-naïve patients with genotype 1 received 4 weeks of treatment and the other 8 groups were to receive 6 weeks but after suboptimal outcomes treatment was extended to 8	Primary: rate of SVR at 12 weeks after the end of therapy (SVR12)	-SVR achieved in 4 of 15 patients (27%) who were treatment-naive with HCV genotype 1 without cirrhosis after 4 weeks. -SVR achieved in 14 of 15 patients (93%) who were treatment-naïve with genotype 1 without cirrhosis, in 13 of 15 (87%) treatment-naïve with cirrhosis, 15 of 18 (83%) treatment-naïve with genotype 3 with cirrhosis, and 20 of 30 (67%) with genotype 1 who failed a previous regiment after 6 weeks. SVR achieved in 17 or 17 patients (100%) with genotype 1 and 19 of 19 (100%) with genotype 3 and cirrhosis who failed pegylated interferon plus riboviron after 8 weeks.	-Eight weeks of treatment with sofosbuvir/ velpatasvir/ and GS-9857 produced an SVR12 in most treatment-naïve or previously treated patients with HCV genotype 1 or 3 infections, including those with compensated cirrhosis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			weeks in treatment-experienced			
Jacobson et al[240] 2017 **LOE-2**	2 phase 3, randomized, open-label non-inferiority trials sofosbuvir/ velpatasvir voxilaprevir (400/100/100mg) for 8 weeks or sofosbuvir/ velpatasvir (400/100mg) for 12 weeks (POLARIS-2 and POLARIS-3)	POLARIS-2: N=882 POLARIS-3: N=219	-Patients ≥18 years old with documented HCV infection who had not been previously treated with DAA POLARIS-2: HCV genotypes 1, 2, and 4 POLARIS-3: genotype 3	-Rate of SVR at 12 weeks after the end of therapy (SVR12)	-POLARIS-2: SVR was 95% (95% CI 93 to 97) among patient receiving 8 weeks of sofosbuvir/ velpatasvir/ voxilaprevir and 98% (95% CI 96 to 99) among those receiving 12 weeks of sofosbuvir/ velpatasvir. 8 weeks did not meet the pre-specified criteria for noninferiority to 12 weeks. -POLARIS-3: SVR was 96% in both treatment groups (95% CI 91 to 99%) which was significantly superior to the performance goal of 83% (P<0.001 for both groups)	-Did not establish sofosbuvir/ velpatasvir/ voxilaprevir for 8 weeks was noninferior to sofosbuvir/ velpatasvir for 12 weeks, but the two regimens had similar rates of SVR in patients with HCV genotype 3 and cirrhosis.
Kanda et al[241] 2017 **LOE-2**	Retrospective cohort study ledipasvir/ sofosbuvir (90/400mg)	N=240 12 weeks	-Japanese patients ≥20 years old infected with HCV with genotype 1	-Rate of SVR at 12 weeks after the end of therapy (SVR12)	-SVR12 was achieved in 136 of 138 (98.6%) of patients who were treatment-naïve and 100 of 102 (98%) of patients who were treatment-experienced	-Combination of ledipasvir plus sofosbuvir for 12 weeks is a potential therapy for HCV GT1 patients.
Lawitz et al[242] 2017 **LOE-2**	Single center, phase 2, open label study	N=49	-Patients ≥18 years old with documented HCV genotype 1 infection who	-Rate of SVR at 12 weeks after the end of therapy (SVR12) Virologic failure, viral	-24 of 24 patients (100%) receiving sofosbuvir/ velpatasvir/ voxilaprevir and 24 of 25 (96%) receiving sofosbuvir/ velpatasvir/ voxilaprevir with RBV achieved	-Results suggested 12 weeks of treatment with a fixed-dose combination of

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	sofosbuvir/ velpatasvir/ voxilaprevir (400/100/100mg) daily with or without ribavirin BID	12 weeks	previously failed to achieve SVR on a DAA-based regimen	resistance	SVR12 -1 patient had virologic relapse	sofosbuvir/ velpatasvir/ voxilaprevir was effective and well tolerated among patients with genotype 1 infection who had previously failed a DAA-based regimen.
Lawitz et al[243] 2016 **LOE-2**	Multicenter, phase2, open label sofosbuvir/ velpatasvir (400/100mg) plus GS-9857 (100mg) once daily for 6 to 12 weeks plus ribavirin for 1 treatment group	N=197 6 to 12 weeks	-Patients ≥18 years old with documented HCV genotype 1 infection who previously failed to achieve SVR on a DAA-based regimen Cohort 1: Treatment naïve patients Cohort 2: Patients previously treated with regimens that contained a	-Rate of SVR at 12 weeks after the end of therapy (SVR12) -Proportion of patients with virologic failure	-SVR12 rates treatment-naïve: • Without cirrhosis were 71% (24 of 34; 95% CI 53 to 85) receiving 6 weeks of treatment • Without cirrhosis were 100% (36 of 36; 95% CI 90 to 100) receiving 8 weeks of treatment • With cirrhosis were 94% (31 of 33; 95% CI 80 to 99) receiving 8 weeks of sofobsuvir/ velpatasvir plus GS-9857 • With cirrhosis were 81% (25 of 31; 95% CI 63 to 93) receiving 8 weeks of sofobsuvir/ velpatasvir plus GS-9857 with ribavirin	-Eight weeks of treatment with sofosbuvir/ velpatasvir plus GS-9857 was found to be safe and effective in treatment naïve patients. Twelve weeks was safe and effective in patients previously treated with DAAs.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			NS5A inhibitor alone, or 2 or more classes of DAAs.		-SVR12 rates previously treated with DAA-containing regimen(s): • 100% (31 of 31; 95% CI 89 to 100) in patients without cirrhosis receiving 12 weeks of treatment • 100% (32 of 32; 95% CI 89 to 100) in patients with cirrhosis receiving 12 weeks of treatment -18 patients with virologic failure relapsed	
Petta et al[244] 2017 **LOE-2**	Prospective, longitudinal, observational study of a compassionate use program ombitasvir/ paritaprevir/ and ritonavir (25/150/100mg) QD and dasabuvir (250mg) BID	N=762 s in the ITT population and N=728 in the PP population 12 or 24 weeks	-Patients ≥18 years old with documented HCV genotype 1 or 4 infection with compensated cirrhosis at a high risk of decom-pensation	-Rate of SVR at 12 weeks after the end of therapy (SVR12) Secondary: percentage of patients with virological breakthrough during treatment or relapse after treatment	-728 (96%) of 762 patients in the ITT population with cirrhosis achieved SVR12 after 12 or 24 weeks of ombitasvir/ paritaprevir/ ritonavir, with or without dasabuvir, plus ribavirin.	-The efficacy and safety profiles of ombitasvir/ paritaprevir/ and ritonavir, with or without dasabuvir, plus ribavirin in patients with HCV genotype 1 or 4 infection and advanced, compensated cirrhosis in a real-world setting are the same as those from clinical trials.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Saxena et al[245] 2017 **LOE- 2**	Multicenter, longitudinal clinical care treatment cohort sofosbuvir/ ledipasvir (SOF/LDV) ± RBV, sofosbuvir/ daclatasvir (SOF/ DAC) ± ribavirin, and ombitasvir/ paritaprevir/ ritonavir + dasabuvir (ProD) ± RBV	N=415	-Patients ≥18 years old with documented HCV and liver transplant (LT), kidney transplant (KT), or dual liver transplant (DLK) recipients	-Rate of SVR at 12 weeks after the end of therapy (SVR12)	-397 patients (95.7%) achieved SVR12: 96.3%, 94.6%, and 90% among LT, KT, and DLK transplant recipients.	-LT, KT, and DLK patients across a spectrum of liver and kidney disease severity achieved high rates of SVR12 with DAA therapy. SOF/LDV was the most commonly used regimen. Ribavirin did not influence SVR rates.
Sulkowski et al[246] 2017 **LOE-2**	Open-label, phase III, single-arm, response-guided treatment daclatasvir (DCV) doses of 30, 60, or 90mg once daily plus weight-based RBV and once-weekly PegIFN 180µg for 24 weeks.	N=301	-Adults aged 18 to 70. HCV treatment-naïve patients coinfected with HIV-1 and HCV GT-1	-Eate of SVR at 12 weeks after the end of therapy (SVR12) Secondary: virologic failure and resistance	-224 (74%) patients achieved SVR12 and the lower bound of the 95% CI was higher than the historic SVR rate with PegIFN/RBV alone (70 vs. 29%). -SVR12 rates were similar regardless of DCV dose: 30mg 75% (99/132), 60mg 72% (28/39), and 90mg 72% (76/106). -51 (17%) of patients met the protocol defined criteria for HCV virologic failure. -34 patients had resistance-associated variants.	-DCV plus PegIFN/RBV for 24 weeks in patients coinfected with HIV-1 and HCV genotype-1 resulted in higher rate of SVR compared with PegIFN/RBV treatment alone, without compromising safety or HIV virologic control. Flexibility of DV dosing (30, 60, or 90mg/day) may allow for options in

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						patients with drug interactions between HCV DAAs and antiretrovirals.
Waked et al[247] 2016 **LOE-2**	Phase 3, multicenter, open-label, partly randomized trial (AGATE-II) ombitasvir/ paritaprevir, ritonavir (25/150/100mg) QD plus weight-based ribavirin for 12 or 24 weeks.	N=160 without cirrhosis received 12 weeks and patients with cirrhosis received 12 or 24 weeks.	-Patients ≥18 years old with chronic HCV genotype 4 infection. Patients were HCV treatment-naïve or treatment-experienced with interferon-based regimens.	-Rate of SVR at 12 weeks after the end of therapy (SVR12) -On-treatment virologic failure and post-treatment relapse	-94 (94%; 95% CI 88 to 97) of 100 patients in the without cirrhosis group, 30 (97%; 84 to 99) of 31 patients in the cirrhosis 12-week treatment group, and 27 (93%; 78 to 98) of 29 patients in the cirrhosis 24-treatement group achieved SVR12. -Patients without cirrhosis: 4 patients experienced virologic failure and 1 patient experienced relapse -Patients with cirrhosis in 24-week treatment group: 1 patient experienced on-treatment virologic breakthrough	-Treatment duration of 12-weeks, with interferon-free, direct-acting antiviral regimen of ombitasvir/ paritaprevir/ and ritonavir plus ribavirin achieved high SVR12 rates in patients with and without cirrhosis. Completing 24 weeks of treatment in patients with cirrhosis did not show an SVR advantage.
Welzel et al[248] 2017 **LOE-2**	Multicenter, open-label, single-arm, phase 3b study (GARNET)	N=166	-Patients ≥18 years old with chronic HCV genotype 1b infection who were previously untreated patients	-Rate of SVR at 12 weeks after the end of therapy (SVR12) Secondary: On-treatment virological failure and post-treatment relapse	-162 (98%; 95% CI 95.3 to 99.9) of 166 patients achieved SVR12. -Two patients with HCV genotype 1b had virologic failure.	-The 8-week, direct-acting antiviral, ribavirin-free treatment option ombitasvir, paritaprevir, and ritonavir, plus dasabuvir, is well

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	ombitasvir, paritaprevir, and ritonavir QD (25/150/100mg) plus twice daily oral dasabuvir 250mg for 8 weeks	8 weeks				tolerated and highly efficacious in previously untreated patients infected with HCV genotype 1b without cirrhosis.
Wyles et al[249] 2017 **LOE-2**	Phase II/III, multipart, open-label study (TURQUOISE-I) ombitasvir/ paritaprevir/ ritonavir (OBV/PTV/r) (25/150/100mg) and dasabuvir (DRV) 800mg once daily or 600mg twice daily with ribavirin	N=22 12 weeks	-Adults aged 18 to 70. HCV genotype 1 infection in HIV-1 coinfected patients on darunavir. Treatment naïve or peg-interferon/RBV treatment-experienced.	-Rate of SVR at 12 weeks after the end of therapy (SVR12) -On-treatment virological failure, post-treatment relapse, maintenance of plasma HIV-1 RNA suppression, SVR12 in DRV QD arm compared to DRV BID arm	-SVR12 was achieved by 100% (22 of 22) of patients. There were not treatment relapses and there was no difference in SVR between patients taking QD versus BID DRV. -Transient HIV viremia occurred in 22% (5 of 22) patients during the treatment period. Two patients taking QD DRV and 3 patients taking BID DRV.	-HIV coinfected patients on a stable regimen containing DRV/r 800/100mg daily could be treated with OBV/PTV/r plus DSV plus RBV for their HCV without an increased risk of HIV virologic failure.
Kwo et al[255] 2017 **LOE-2**	2 Phase II, open-label, multicenter, dose-ranging studies (SURVEYOR-I/II) SURVEYOR-I (GT 1,4-6) SURVEYOR-II (GT 2,3) Part 1 of both: **GT1**-GLE 200mg + PIB 120mg OR 40mg **GT2**-GLE 300mg + PIB	N=449 36 weeks	-Patients aged 18-70 years with HCV genotype 1-6 and HCV RNA level >10,000 IU/mL at screening, either treatment-naïve or experienced with RBV or	Primary: percentage of patients who achieved SVR12 Secondary: percentage of patients with SVR at post-treatment week 4, on-treatment virologic failure, and post-treatment	Part I results: -GT1 SVR12 rates: • 97% (38/39, 95% CI 87-100) with GLE 200mg+PIB 40mg • 100% (40/40, 95% CI 91-100) with GLE 200mg+PIB 120mg -GT2 SVR12 rates: • 96% (24/25, 95% CI 80-99) with GLE 300mg+PIB	-SURVEYOR Part I concluded with the optimized dosing regimen of GLE 300mg plus PIB 120mg, which was used in Part II -Even though there is already another pangenotypic option currently

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	120mg, GLE 200mg +PIB 120mg ± weight-based RBV GT3-GLE 300mg + PIB 120mg OR GLE 200mg + PIB 120mg ± weight-based RBV OR GLE 200mg + PIB 40mg Part 2 of both studies: GLE 300mg + PIB 120mg for 8 weeks for GT1,2,3 (treatment-naïve), and 12 weeks for GT3 (treatment-experienced), 4, 5		peginterferon, excluding DAA use, and lack of cirrhosis Exclusions: Evidence of HBV or HIV coinfection or more than one genotype at screening	relapse Other: resistance analysis for virologic failure, safety	120mg, • 100% (24/24, 95% CI 86-100) with GLE 200mg+PIB 120mg ±RBV • No virologic failures -GT3 SVR12 rates: • 83% (25/30, 95% CI 66-93) with GLE 200mg+PIB 40mg • 93% (28/30, 95% CI 79-98) with GLE 200mg+PIB 120mg • 94% (29/31, 95% CI 79-98) with GLE 200mg+PIB 120mg+RBV • 93% (28/30, 95% CI 79-98) with GLE 300mg+PIB 120mg Part II results: -GT4-6 SVR12 rates after 12 weeks of treatment: 100% (34/34, 95% CI, 90-100) -GT3 treatment-experienced SVR12 rate after 12 weeks of treatment: 92% (22/24, 95% CI 74-98); -GT1 SVR12 rate after 8 weeks of treatment: 97% (33/34, 95% CI 85-99) -GT2 SVR12 rate after 8 weeks of	available, the advantage of GLE+PIB is its use in patients regardless of baseline polymorphisms and shorten treatment durations to 8 weeks in those without cirrhosis. This has the potential to increase adherence, tolerability, and access.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					treatment: 98% (53/54, 95% CI 90-100) -GT3 treatment naïve SVR12 rate after 8 weeks of treatment: 97% (28/29, 95% CI 83-99) - No virologic failures were seen for GT1-6 in Part II Resistance Analysis for virologic failure: -10 out of 449 patients (2%) experienced either on-treatment or post-treatment failure. - 9 of these had HCV GT3a and 1 had GT1a infections. - Of the 9 GT3a patients, the treatment-emergent substitution of Y93H was frequently present at the time of failure, although the impact could not be determined. Safety: -70% of patients (319/449) experienced at least one side effect, with the majority being mild in severity, including fatigue, headache, and nausea (≥10%). These side effects were higher in frequency for those with RBV-containing regimens. - 3 patients (0.7%) discontinued	

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					the medication due to side effects.	
Gane et al[262] 2016 **LOE-2**	Phase II, open-label, multicenter study (Subset of SURVEYOR-I (GT1)/II (GT3)) GT1: GLE 200mg+PIB 120mg for 12 weeks GT3: GLE 300mg + PIB 120mg± 800mg RBV for 12 weeks * 4 treatment-experienced patients' durations were extended to 16 weeks	N=52 40 weeks	-Patients aged 18-70 years with HCV GT 1 or 3, either treatment-naïve or experienced with RBV or peginterferon, excluding DAA use, and presence of cirrhosis (Child Pugh score ≤6) Exclusions: CrCl <50mL/min, albumin or Hgb <ULN, ALT or AST >5x ULN, platelets <90, or evidence of HBV or HIV coinfection or more than one genotype at screening	-Percentage of patients who achieved SVR12 Secondary: percentage of patients with SVR at post-treatment week 4, on-treatment virologic failure, and post-treatment relapse Other: resistance analysis for virologic failure, safety	-GT1 SVR12 rates: • 96% (26/27, 95% CI 82-99) with GLE 200mg + PIB 120mg • 95% (20/21) of GT1a and 6 GT1 treatment-experienced patients -GT3 SVR12 rates: • 96% (27/28, 95% CI 82-99) with GLE 300mg + PIB 120mg • 100% (24/24) of treatment-naïve and 75% (3/4) of treatment-experienced patients • 100% (27/27, 95% CI 88-100) with GLE 300mg + PIB 120mg + RBV 800mg -100% SVR12 rate was achieved for both GT1 and GT3 patients without baseline substitutions. -Side effects were experienced in 74% (61/82) of patients, being mild-to-moderate in severity. These included headache (15%), diarrhea (13%), and fatigue (11%); percentages of these were increased with RBV-containing	-The results of these Phase II trials suggest that the once-daily, RBV-free regimen of GLE plus PIB is a viable option to achieve high SVR12 rates for patients with GT1 or GT3 with compensated cirrhosis

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					regimens. -5 serious adverse effects were reported with only 1 having a reasonable possibility of being drug-related	
Poordad et al[256] 2017 **LOE-2**	Phase II, randomized, open-label, multicenter study (MAGELLAN-1) ArmA: GLE 200mg + PIB 80mg (n=6) ArmB: GLE 300mg + PIB 120mg + RBV 800mg (n=22) ArmC: GLE 200mg + PIB 120mg (n=22)	N=50 36 weeks	-Patients aged 18-70 years with HCV genotype 1, without cirrhosis but treatment-experienced with a prior DAA-containing regimen (at least 1 month prior) Exclusions: HBV or HIV coinfection	-Percentage of patients who achieved SVR12 in ITT population Other: HCV resistance analysis, safety	- SVR12 was achieved in 92% (46/50, 95% CI 81-97) of patients treated with GLE+PIB ± RBV for 12 weeks in the ITT analysis. - In ArmA, patients received an overall lower dose of GLE+PIB, which 100% of the 6 patients achieved SVR12. -95% of patients (21/22, 95% CI 78-99) in ArmB achieved SVR12; however, in ArmC, only 86% of patients (19/22, 95% CI, 67-95) achieved SVR12. -Virologic failure rates were the same for both Arms B&C with or without RBV (1/22, 5%). -In a modified ITT analysis, the SVR12 rates increased to 100%, 95%, and 95% for Arms A, B, &C, respectively.	-High SVR rates with or without concomitant administration of RBV was demonstrated in the once-daily, well-tolerated regimen of GLE and PIB for patients without cirrhosis with genotype 1 and prior treatment with DAAs. The resistance analysis suggests that GLE and PIB is effective for those regardless of the presence of one or more resistance-associated polymorphisms.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-Patients with baseline polymorphisms in NS3, NS5A only, both, or none had SVR12 rates of 100% (14/14), 91% (10/11), 93% (14/15), and 100% (10/10) with 15% threshold, respectively. -Mild to moderate side effects (headache, fatigue, nausea, and insomnia in ≥10% of patients) were reported in 84% of patients, even more so in the RBV-containing regimens.	
Zeuzem et al[257] 2016 **LOE-2**	Multicenter, randomized, open-label, phase 3 study glecaprevir/ pibrentasvir	N=703 8-12 weeks	-Patients ≥18 years old, HCV genotype-1 infected patients with or without HIV-1 co-infection and without cirrhosis in treatment naïve or experienced patients	-SVR12 rate (lower bound of two-sided 95% CI interval is greater than the historical 91% SVR12 rates) and noninferiority (5% margin) in SVR12 of 8-12 weeks -Virologic failure and post-treatment relapse	-99-100% of GT-1 infected patient without cirrhosis achieved SVR12 with 8 or 12 weeks of glecaprevir/pibrentasvir -8-week treatment was non-inferior to 12-week treatment	-Ribavirin-free glecaprevir/pibrentasvir regimen achieved high SVR12 rates in 8 weeks for non-cirrhotic patients with HCV GT1 infection, including those with HIV-1 co-infection. **CHC Comments:** This study is not currently published, and the information was extracted from the conference

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						abstract.
Kowdley et al[258] 2016 **LOE-1a**	Randomized, double-blind, placebo-controlled, multicenter, phase 3 study glecaprevir/ pibrentasvir	N=302 12 weeks	-Patients ≥18 years old, non-cirrhotic, HCV genotype-2 infected patients, treatment naïve or treatment experienced	-SVR12 rates	-99% of patients achieved SVR12. -There were no virologic failures.	-Ribavirin-free glecaprevir/pibrentasvir regimen achieved high SVR12 rates with no virologic failures with 12 weeks for non-cirrhotic patients with HCV genotype-2 infection. **CHC Comments:** This study is not currently published, and the information was extracted from the conference abstract.
Foster et al[259] 2017 **LOE-1**	Non-inferiority, randomized study glecaprevir/ pibrentasvir Vs sofosbuvir plus daclatasvir	N=348 8 or 12 weeks	-Patients ≥18 years old, non-cirrhotic, HCV genotype-3 infected patients, treatment naïve	-Non-inferiority of SVR12	-12 weeks of glecaprevir/pibrentasvir (95% SVR12) was non-inferior to 12 weeks of sofosbuvir plus daclatasvir (97% SVR12) -8 weeks of glecaprevir/pibrentasvir was non-inferior to 12 weeks of	-Glecaprevir/pibrentasvir achieved high efficacy in non-cirrhotic, treatment-naïve patients with chronic HCV GT3 infection.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					glecaprevir/pibrentasvir. SVR12 was 95% after 8 weeks of glecaprevir/pibrentasvir.	**CHC Comments:** This study is not currently published and the information was extracted from the conference abstract.
Asselah et al[260] 2016 **LOE-2**	Multicenter, open-label, single-arm, phase 3 study glecaprevir/ pibrentasvir	N=121 12 weeks	-Patients ≥18 years old, treatment naive or treatment experienced, chronic HCV GT4, 5, or 6 infection without cirrhosis	-Number and percentage of patients achieving SVR12 -Virologic failure and post-treatment relapse	-99% of genotype 4-6 patients (120/121) achieved SVR12. -No virologic failures.	- Glecaprevir/pibrentasvir achieved high efficacy in 12 weeks for non-cirrhotic patients with HCV genotype 4—6 infection. **CHC Comments:** This study is not currently published and the information was extracted from the conference abstract.
Wyles et al[261] 2016 **LOE-2**	Efficacy and safety of	N=131	-Patients ≥18 years old, treatment experienced, chronic HCV GT	-Number and percentage of patients achieving SVR12	-SVR12 rates ≥96% in treatment naïve and treatment experienced patients with cirrhosis following 12 or 16 weeks.	- Glecaprevir/pibrentasvir achieved high efficacy in 12 weeks or 16 weeks for

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	glecaprevir/ pibrentasvir	12 or 16 weeks	3 and/or cirrhosis		-SVR12 rate 96% in treatment experienced patients without cirrhosis following 16 weeks, or 91% after 12 weeks.	genotype 3 infected patients with prior treatment experience and/or compensated cirrhosis. **CHC Comments:** This study is not currently published, and the information was extracted from the conference abstract.
Asselah et al[266] 2017 **LOE-2**	Retrospective analysis sofosbuvir 400mg/ velpatasvir 100mg daily	N=501 12 weeks	Adults with chronic Hepatitis C and advanced fibrosis or compensated cirrhosis with genotypes 1-6	-Rates of SVR12 -Laboratory assessments of liver disease -Safety	SVR12 rates: - Overall: 98% achieved SVR12 (490/501, 95% CI 96-99) - Those with cirrhosis: 96% (212/220) - Those with advanced fibrosis: 99% (278/281) - Treatment-naïve: 98% (306/311) - Treatment-experienced: 97% (184/190) - Genotypes 2, 4, 5, or 6: 100% - Genotype 1: 98% (167/170) + cirrhosis: 99% (72/73) - Genotype 3: 91% (73/80) - IL-28B genotype: non-CC 97%	- The authors concluded that sofosbuvir and velpatasvir is highly effective as a pangenotypic treatment in patients with concomitant HCV and compensated cirrhosis or advanced fibrosis. **CHC Comments:**

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					(318/327) & CC 99% (169/171) - Baseline NS5A ≥15%: with 96% (134/139) & without 98% (355/361) - There were no virologic failulres while on treatment, the 10 patients who did not achieve SVR12 had virologic relapse after treatment. - Median values of platelets, albumin, and total bilirubin improved from baseline to post-treatment week 4. The percentage of those with an APRI score of >2.0 were 31% (154/501) at baseline and only 1% (5/426) at 4 weeks post-treatment. - The most common adverse events were headache (31%), fatigue (21%), nausea (13%), and nasopharyngitis (11%). There were 8 patients with serious side effects, however none were related to the treatment. No patients discontinued the medication due to side effects.	- A limitation of this study is the uneven distribution of HCV genotypes (specifically genotypes 5 and 6, accounting for <5% of cases), however they represent a small number of cases.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Butt et al[267] 2017 **LOE-2**	Propensity score-matched retrospective analysis paritaprevir/ ritonavir, ombitasvir, dasabuvir (PrOD) Vs. sofosbuvir/ ledipasvir (LDV/SOF) Vs. propensity score matchs (1:1)	N=13,940 PrOD (n=1473) LDV/SOF (n=5497) Matchs (n=6970) 18 months	-Patients with HCV who were started on PrOD or LDV/SOF regimen from the ERCHIVES national cohort Exclusions: HIV coinfection, positive Hepatitis B surface antigen test, hepato-cellular carcinoma	-Survival	-Proportion of subjects who died was higher in those who were untreated compared to either treatment group (PrOD 0.3%; LDV/SOF 1.4%, controls 2.5%, p<0.001). -In comparison of treatment groups to controls in a Kaplan-Meier curves, a significantly larger proportion of treated patients were alive at 18 months of follow-up. -Factors associated with higher mortality: increasing age, presence of cirrhosis, diabetes, CKD, or anemia at baseline -Factors associated with lower mortality: black race, increasing HCV RNA, treatment (HR 0.43). Attaining SVR was also associated with significantly lower mortality (HR 0.57).	-The treatment of HCV with PrOD or LDV/SOF regimens and SVR attainment were associated with significantly reduced mortality within the first 18 months of treatment.
Chayama et al[268] 2017 **LOE-1b**	Phase 3, open-label, multicenter, randomized noninferiority study (CERTAIN-1)	N=219 Substudy 1: -Arm A=129 -Arm B=52 Substudy 2=38	Substudy 1: Adults with genotype 1 HCV without cirrhosis	Substudy 1- Primary endpoint: -Noninferiority achieving SVR12 Secondary endpoint:	Substudy 1- -Difference in SVR12 achievement between 2 treatment groups was -0.9% (95% CI, -2.8%, 0.9%), which demonstrated noninferiority	-The authors concluded that G/P demonstrated high efficacy and favorable tolerability in

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	Substudy 1: GLE/PIB 300/120mg daily for 8 wks (Arm A) Vs. OBV/PTV/r 25/150/100mg daily for 12 wks (Arm B) Substudy 2: GLE/PIB 300/120mg daily for 12 wks	24-36 weeks (followed 12 weeks post-treatment)	Substudy 2: Adults with genotype 1 HCV with compensated cirrhosis -All were required to be treatment/ DAA-naïve or failed prior IFN/peg-IFN +/- RBV therapy -Exclusion: HBV or HIV co-infection or current/past clinical evidence of Child-Pugh B or C, de-compensated liver disease	-Percentage of all patients achieving SVR12 with Y93H polymorphism Substudy 2- Primary endpoint: -Percentage achieving SVR12 Secondary endpoint: -Percentage of patients with virologic failure during treatment and relapse post-treatment -PK results -Safety	-In the ITT population with the Y93H polymorphism, 99.1% of patients in Arm A and 100% in Arm B achieved SVR12 with no virologic failures. The polymorphism did not impact the outcome. -57% and 67% of patients reported an adverse effect in Arm A and Arm B, of which 23% and 27% had at least 1 AE that was deemed drug related, respectively. Naso-pharyngitis was reported by 16% in Arm A and 14% in Arm B. Pyrexia was the only AE that was significantly different between Arm A and B (0% v. 6%, p=0.023). -No serious adverse effects occurred in those treated with G/P; however, 3 patients experienced serious effects, but was not deemed drug related (p=0.023). Substudy 2- -100% of patients with compensated cirrhosis achieved SVR12.	Japanese patients with HCV genotype 1, including those with Y93H polymorphism and with or without cirrhosis. **CHC Comments:** -Conclusions are limited to Japanese patients with HCV genotype 1

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-66% of patients with compensated cirrhosis experienced a side effect with 18% considered drug related. Malaise was reported by 11%. -There was no drug accumulation observed. -No serious adverse effects occurred.	
Toyoda et al 2018[274] **LOE-2**	Phase 3, open-label, randomized, multicenter, noninferior study (CERTAIN-1 & 2) CERTAIN-2: G/P for 8 weeks (Arm A) Vs. SOF 40mg + weight based RBV for 12 weeks (Arm B) *randomization by prior IFN/peg-IFN experience and HCV RNA viral load	N=154 Arm A=90 Arm B=46 Arm C=18 32-36 weeks (followed 24 weeks post-treatment)	CERTAIN-2: Adults with genotype 2 HCV without cirrhosis CERTAIN-1 Substudy 2: Adults with genotype 2 HCV with compensated cirrhosis -Exclusion: HBV or HIV co-infection or current/past clinical evidence	CERTAIN-2: Primary endpoint: -Noninferiority achieving SVR12 Secondary endpoint: -Percentage of patients with virologic failure during and relapse post-treatment -Impact of Y93H polymorphism on SVR12 CERTAIN-1: Primary endpoint: -SVR12	CERTAIN-2: -Noninferiority was met; the difference between groups was 4.3% (95% CI, -3.5 – 12.1). 97.8% of Arm A patients and 93.5% of Arm B patients achieved SVR12. -There were no virologic failures in Arm A with 2 relapses by post-treatment week 12 in Arm B. -Baseline polymorphisms did not have an impact of SVR12, since there were no virologic failures. -48% of Arm A patients and 76% of Arm B patients experienced any AE (p=0.002), whereas only 18% and 50% were attributed to the	-8 weeks of GLE/PIB demonstrated non-inferiority with a 12-week regimen of SOF/RBV; GLE/PIB was a well tolerated, highly effective treatment regimen for those infected with HCV genotype 2 with and without cirrhosis. **CHC Comments:** -Conclusions are limited to Japanese patients with HCV genotype 1

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	CERTAIN-1 substudy 2: G/P for 12 weeks (Arm C)		of Child-Pugh B or C, de-compensated liver disease, or CrCl <30mL/ min (CERTAIN 1) or <50mL/ min (CERTAIN 2)	-PK results -Safety	drug (p<0.001), respectively. Anemia, hyperuricemia, and blood bilirubin increase was significantly greater in Arm B versus A (p<0.05). -2 serious events occurred in both Arms, however only 1 in Arm B was deemed drug related. CERTAIN-1: -100% of patients with compensated cirrhosis achieved SVR12. -67% of patients reported an AE, but only 39% was drug related. Pruritis (22%), nasopharyngitis (11%) and increased blood bilirubin (11%) were the top three AEs reported.	
Flisiak et al[269] 2017 **LOE-2**	Prospective, single-arm, observational, multi-center study (HARVEST) ledipasvir/ sofosbuvir (LDV/SOF) +/- (weight-based) RBV	N=86 8, 12, 24 weeks (based on treating physician	-Adults with chronic HCV infection that were either treatment-naïve or experienced	Endpoints: -Proportion of patients with SVR12 -AEs from baseline to 30 days post-treatment	-94.2% (81/86) of patients achieved SVR12. -Despite having high baseline viral loads, 100% of patients treated for 8 weeks achieved SVR12, while only 93.4% achieved SVR12 when treated for 12 weeks. -Depending on baseline	-Treatment with ledipasvir/ sofosbuvir with or without ribavirin is a safe option with good efficacy, especially in those with advanced liver disease or in treatment-

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
		discretion) *8 weeks was reserved for genotype 1b and no/moderate fibrosis			characteristics and RBV use, SVR12 rates ranged from 75-100%. 100% of female, non-cirrhotic patients achieved SVR12, however in patients with cirrhosis, decreased platelet count, hypoalbuminemia, or Child-Pugh B or C had <90% SVR12 rate. -There were 5 virologic failures, which were all male, cirrhotic, and had genotype 1b. Of the 5 failures, 2 were virologic breakthrough and 3 had virologic relapse post-treatment. -Adverse effects were observed in 80.2% of patients and were mild, in general. Three most common AEs seen were fatigue (22.1%), headache (15.1%), and arthralgia (7%). Hemoglobin <10g/dL was seen in 16.2% of patients who were treated with RBV, but only 2% in those who were not treated with RBV.	experienced patients. **CHC Comments**: -Limitations of this study include the small number of participants and the majority of patients had genotype 1b (82.6%) and the variability in treatment durations.
Forns et al[270] 2017 **LOE-2**	Phase 3, single-arm, open-label, multi-center, international study (EXPEDITION-1)	N=146 1a= 48 (33%) 1b=39 (27%) 2=34 (23%) 4=16 (11%)	-Adults with chronic HCV infection who were DAA-naïve	Primary endpoint: -Achievment of SVR12 Secondary endpoint:	-In the intention-to-treat population, 99% of patients achieved SVR12. -One patient had a relapse at 8	-A 12-week regimen of GLE/PIB resulted in high efficacy and safety in patients with

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	GLE/PIB daily for 12 weeks	5= 1 (1%) 6=7 (5%) 36 weeks (followed for 24 weeks post-treatment)	Exclusions: HBV or HIV co-infection	-Proportion of patients with on-treatment virological failure during and relapse post-treatment -Safety	weeks post-treatment. This patient has genotype 1a infection with a history of non-response to peg-IFN plus RBV. -69% of patients experienced an AE, with 64% being mild in nature (fatigue and headache). No patients discontinued due to side effects. -8% of patients had serious AEs, although none were deemed drug related.	genotypes 1, 2, 3, 4, 5, and 6 infections and compensated cirrhosis. **CHC Comments:** -This study did not have patients with genotype 3. -Funder (Abbvie) played a role in study design, data collection, data analysis, and interpretation.
Kutala et al[271] 2017 **LOE-2**	Retrospective, non-interventional, single-center study SOF 400mg + RBV 1200mg [Arm A] Vs SOF 400mg + daclatasvir (DCV) 60mg [Arm B] Vs SOF 400mg + simeprevir (SIM) 150mg +/- RBV 1200mg [Arm C]	N=383 36 weeks (followed for 24 weeks post-treatment)	-Patients with chronic HCV treated between November 2013 and July 2015 with fibrosis stage F3-F4	Primary outcome: -Virologic response (SVR12) Secondary outcome: -Safety	-132 (82%) of Arm A, 132 (92%) of Arm B, and 62 (79%) in Arm C achieved SVR12. Arm B demonstrated higher efficacy than the Arm A (p=0.035) and Arm C (p=0.009). -Fatgiue (27%), headache (18%), and nausea (19%) were the most common adverse effects reported, which were not drug-related. The most common grade 3 laboratory abnormalities were low hemoglobin levels and platelet counts, these were associated	-An all-oral, SOF-based regimen plus daclatasvir demonstrated high efficacy and safety in patients with both fibrosis F3 and cirrhosis F4. **CHC Comments:** -Limitations include that a subset of patients (<27%) were included

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					with RBV use. -Patients with non-genotype 1 and fibrosis F3, SVR rates were consistently high. SVR in treatment-naïve patients were comparable between Arms and consistently high. -SVR rates varied with treatment regimen and degree of cirrhosis; lowest rate was observed with Arm C at 73%. The overall rate was 78% in cirrhotic patients compared to 91% in fibrosis F3. -Baseline serum albumin, fibrosis, age, and gender were independently associated with SVR12.	without a liver biopsy, the treatment regimen was at the provider's discretion, and not all regimens contained RBV.
Buggisch et al[272] 2018 **LOE-2**	Multicenter, retrospective, non-interventional registry	N=2,404 (ITT1 – safety population) N=2,066 (ITT2 – effective-ness population)	-Patients were ≥18 years who were infected with HCV that were in the German Hepatitis C-Registry Co-infection with HIV: 20.5%	Primary endpoint: -Proportion of patients with SVR12 Secondary endpoint: -Safety Exploratory analysis	-SVR12 rates: 84.6% (overall), 85.1% (ITT1-8 wks), 94% (ITT2-8 wks), 85.5% (ITT1-12 wks), 94.9% (ITT2-12 wks) -Patients experienced more side effects in the 12 weeks (50.4%) versus 8 weeks of treatment (40.4%). There were low and comparable rates of discontinuation between the 2	-Overall, a regimen of LDV/SOF is a well-tolerated, safe, and highly efficacious treatment option. An 8-week regimen had comparable efficacy with 12-week regimen, therefore a shorter

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	ledipasvir/ sofosbuvir daily for 8 weeks (n=835) Vs LDV/SOF daily for 12 weeks (n=1,231)	8-12 weeks	Opioid substitution therapy: 17.6% Exclusions: pregnancy (patient or female partner of male patient), women of child-bearing age or nursing		groups. -SVR12 was associated with the absence of cirrhosis (OR 0.14, p=0.015), and female gender (OR 4.04, p=0.024). -Relapse rates were low and similar between treatment groups (1.5% relapsed post-treatment; 1.4% after 8 weeks and 1.5% after 12 weeks of treatment). -Baseline factors associated with high rates include baseline viral load, age, HIV co-infection, opioid substitution therapy, and HCV genotype – factors were independent of SVR12.	treatment duration can be recommended to reduce costs of therapy. **CHC Comments:** -Limitations include the lack of randomization due to the treatment regimen being at the provider's discretion.
Rosenthal et al[273] 2017 **LOE-2**	Multicenter, open-label, double-arm, nonrandomized, phase 2 pilot trial LDV/SOF daily Cirrhotic – 24 wks Non-cirrhotic – 12 wks	N=68 42-48 weeks	-Adults co-infected with HIV/HCV genotype-1 infection. Other inclusion criteria was failure or premature discontinuation with peg-IFN/RBV and first-generation	Primary endpoint: -SVR12 Secondary endpoints: -SVR4 & SVR24 -Virological response at weeks 1, 2, 4, 12, 16, 20, 24, 30, 36, 42, plus 48 -Safety -PK -Patient-reported	-Of the 68 enrolled, 65 (95.6%) achieved SVR12 and SVR24 (p<0.001). -All patients reported at least 1 adverse effect with most being mild to moderate in severity (most common: fatigue, hypertension, and headache). 11 patients had serious side effects, including 1 patient with thrombocytopenia which was drug-related and 1	-This study demonstrated that LDV/SOF has high efficacy in protease inhibitor-experienced patients with HCV/HIV co-infection, including patietns with cirrhosis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			PI, patients on stable antiretroviral treatment, and on HCV treatment for at least 3 months Exclusions: Child-Pugh B or C cirrhosis, or history of de-compensated cirrhosis, HBV co-infection, or any DDs with the medications	outcomes	patient discontinued the medication due to GI bleeding. Other reported side effects are mild proteinuria, hypophosphatemia, blood bicarbonate decrease, and hypokalemia in 54.4%, 50%, 29.4%, and 13.2%, respectively. A decrease in bicarbonate was seen more frequently in cirrhotic patients than non-cirrhotic patients (44.4% vs 19.5%, p=0.03). -Although not significant, there was a trend for more rapidly undetectable HCV viral loads in non-cirrhotic compared to cirrhotic patients. -CD4 cell counts were stable throughout treatment and follow-up; 1 patient had a HIV virological rebound after discontinuing antiretroviral treatment at week 28.	**CHC Comments:** -Limitations include the restriction of permitted antiretroviral regimens, including the use of ritonavir-boosted HIV-1 PIs or cobicistat-boosted evitegravir with tenofovir.
Wyles et al[275] 2018 **LOE-2**	Phase 3, partially randomized, open-label, multicenter study (Part 3 of SURVEYOR-II)	N=132	-Patients were ≥18 years, either treatment- / DAA-naïve or treatment-	Primary endpoint: -SVR12 Secondary endpoints: -Percentage of patients with on-	SVR12 rates: -Treatment-naïve with cirrhosis treated for 12 weeks: 98% (39/40); no virologic failures -Treatment-experienced with cirrhosis treated for 16 weeks:	-Patients treated with GLE/PIB combination regimen for either 12 or 16 weeks was well-tolerated and

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	Arm A: GLE/PIB daily for either 12 wks (cirrhotic and non-cirrhotic) Arm B: GLE/PIB daily for either 16 wks (cirrhotic and non-cirrhotic)	40 weeks	experienced who also had HCV genotype 3 infection Exclusions: -HBV or HCV co-infections or other HCV genotypes	treatment virologic failure and post-treatment relapse -Safety	96% (45/47) -Treatment-experienced without cirrhosis treated for 12 weeks: 91% (20/22) -Treatment-experienced without cirrhosis treated for 16 weeks: 95% (21/22) -Prior SOF treatment: 98% (41/42) -Patients with compensated cirrhosis and those without: 97% (84/87) vs. 93% (41/44) -Patients with baseline NS3 polymorphism and those without: 96% (105/109) vs. 95% (18/19) -Patients with baseline NS5A polymorphism and those without: 97% (68/70) vs. 100% (15/15) -Difference in rates between 12- and 16-week regimens was -4.5% (95% CI, -23.6 to 13.9). There were only 2 relapses and 1 relapse in each arm, respectively. -Fatigue and headache were the most common adverse effects in both treatment arms (22% vs. 19%, respectively); all of the side effects were classified as mild. No patients prematurely discontinued the drug.	associated with high efficacy in both treatment-naïve and experienced patients and/or cirrhosis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-There were only 6 serious ;adverse effects, and none were due to the study drug. No patients had hepatic decompensation events. -All types and side effect frequencies were similar between treatment regimens.	
Grebely et al[282] 2018 **LOE-2**	Phase 4, open-label, single-arm, inter-national, multicenter trial (SIMPLIFY) SOF/velpatasvir daily for 12 weeks	N=103 36 weeks with 6 months, up to 2 years (planned follow-up)	-Adults with chronic HCV infection with genotypes 1-6 that were naïve to NS5A-based HCV therapy and in people who inject drugs (PWID) Exclusions: -HIV co-infection or de-compensated liver disease	Primary endpoint: -Proportion of patients achieving SVR12 Secondary endpoints: -Treatment completion -Treatment adherence -Safety -Changes in drug use during treatment -HCV reinfection	-96% had an end-of-treatment response, and 94% achieved SVR12. There was no difference between those with recent drug use at baseline compared to those without (p=0.684), as well as during HCV treatment (p=0.704). -The overall median adherence was 94%, and 66% of the patients were at least 90% adherent. -83% of patients had at least 1 side effect, which 47% were drug related. The 3 most common adverse effects were fatigue, headache, and nausea. There were 4 deaths during the study period, however they were due to an overdose of illict drugs. -At baseline, most had injected	-The authors concluded that HCV treatment should be offered to PWID, irrespective of ongoing drug use which did not affect achievement of SVR. Recent injection drug use should not be used as a reason to withhold reimbursement of HCV therapy. **CHC Comments:** -Limitations of the study include the small sample size and the lack of genotypes 5 or 6 in

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					drugs in the past month, a quarter had injected at least daily, and more than half were receiving opioid substitution therapy. However, drug use was fairly stable throughout treatment. -There was only 1 case of HCV reinfection (38 person-years of follow-up; reinfection rate 2.6 cases per 100 person-years [95% CI, 0.1-13.8]), although the patient was HCV-negative at the end of treatment but had recurrent viremia at SVR12.	the study population. -Also, important to note that many countries still have restrictions against reimbursement of DAA therapy for those with recent injection drug use (policy varies by state), and many providers may be hesitant to prescribe DAAs in PWID.
Preda et al 2017[281] **LOE-2**	Prospective, national cohort study paritaprevir/ ritonavir, ombitasvir, dasabuvir (PrOD) + weight based RBV	N=2,070 24 weeks	-Adults with HCV genotype 1b infection with cirrhosis. Other inclusion criteria: advanced fibrosis, no significant alcohol consumption in the last 3 months. Patients with	-Percentage of patients achieving SVR -Safety (severe AEs)	-In the ITT population, SVR was achieved in 96.6% (1999/2070); the per-protocol SVR rate was 99.4% (1997/2008). There were 2.7% (55/2070) of patients who did not respond to treatment. -In a multi-variate analysis, lack of interferon pre-treatment (OR 1.7, p=0.02), comorbidities (OR 0.4, p=0.001), increased bilirubin (OR 0.5, p<0.001), prolonged INR (OR 0.3, p=0.007), decreased creatinine clearance (p=0.001), and platelets $<10^5/mm^3$ (OR 0.5,	-Combination treatment with PrOD and ribavirin was generally safe and well-tolerated, as well as an effective regimen even for patients with cirrhosis in this real-life cohort. **CHC Comments:** A noteable limitation of this study was that only

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			HBV co-infection or hepatocellular carcinoma were not excluded but had specific, additional criteria to be included.		p=0.029) were associated with non-response. -2.9% (60/2070) of patients had stopped therapy due to severe adverse events and 1 was lost to follow-up. AEs reported in the study included: hepatic decompensation (n=40), encephalopathy (n=8), allergic reactions (n=3), bacterial infections (n=3), cardiovascular events (n=2), vomiting (n=1), renal failure (n=1), anemia (n=1), fatigue/dizziness (n=1), and worsening of pre-existing mental depression (n=1) which were thought to be associated with therapy. 8 others had non-drug related AEs. -Hepatic decompensation had a mortality rate of 35%. De-compensation mostly occurred in the first month (n=26) or second month (n=9) of therapy. Predictive factors in a multivariate analysis were platelets $<10^5/mm^3$ (OR 2.3, p=0.03), increased bilirubin (OR 3.3, p<0.001), prolonged INR (OR 3.5, p=0.02), and albumin	serious AEs that lead to discontinuation were reported.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					<3.5g/dL (OR 0.4, p=0.03). The mortality rate for encephalopathy and variceal bleeding were 87.5% and 43%, respectively.	
Lim et al[280] 2017 **LOE-2**	Prospective, longitudinal, international, observational study (HCV-TARGET) LDV/SOF Or LDV/SOF/RBV (12-24 weeks)	N=634 (evaluable) N=610 (per protocol – PP) 24-36 weeks	-Adults with HCV genotype 1 infection that had previously failed antiviral therapy and had clinical evidence of cirrhosis -Must have failed prior-IFN based therapy (pegIFN±RBV, BOC+ pegIFN± RBV, TEL+ pegIFN±RBV, SOF+ pegIFN± RBV, or SIM+ pegIFN±RBV) -Included DAA-experienced (27%), history of hepatic de-compensation (40%), or cirrhosis post-	Efficacy Endpoint: -SVR -Safety	-Overall, 93.8% (579/610) of patients achieved SVR12. This includes 12-week regimens resulting in SVR rates of 98% (50/51) of LDV/SOF and 97.1% (68/78) of LDV/SOF/RBV and 24-week regimens with 94.1% (384/408) and 95% (57/60), respectively. -For subgroups, patients with genotype 1a and 1b had similar SVR rates (95.1% vs 95%) and those with history of liver transplant achieved a lower SVR than those without (92.8% vs 95.3%). Patients with a history of hepatic decompensation were more likely to have 24-week regimens but had a lower SVR rate compared to those with compensated cirrhosis (92.2% vs 96.6%). -The addition of RBV or treatment duration did not predict SVR in a multivariate analysis. Predictors of	-Treatment with LDV/SOF with or without ribavirin was found to be both safe and effective in treating treatment-experienced, compensated cirrhotic patients with HCV genotype 1. However, there were no significant differences in SVR rates in 12- or 24-week regimens with or without ribavirin.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			OLT (14%)		greater response found were decompensated cirrhosis (OR 2.41), albumin ≥3.5 (OR 3.15), or total bilirubin ≤ 1.2 (OR 3.34), and predictors of decreased response was male gender (OR 0.49) and the concomitant use of proton pump inhibitors (OR 0.56). -Discontinuation rates between groups with and without RBV were similar at 2.1% and 1.4%, however, AE rates were lower in patients without RBV (73.3%) compared to those with RBV (87.1%). The most common AEs (≥10%) were fatigue, headache, and infections/infestations; anemia was reported in 30.6% of RBV patients and only 1.4% of LDV/SOF only patients.	
Kondili et al[279] 2017 **LOE-2**	Prospective, observational interim analysis Any HCV DAA-based regimen available at the time	N=3,869 Jan 2015-Dec 2016 (end of the period for SVR12 evaluation for	-Patients with HCV that were treated at 1 of 23 clinical centers involved in PITER who were treated with DAA who reached SVR12 from Jan 2015-	Clinical data: -SVR12 rates -Changes in following liver fibrosis stage and/or presence of clinical cirrhosis, Child-Pugh score and complications of severe liver disease if present (ascites,	-95.3% (3,691/3,869) achieved while 3.6% (139/3,869) did not achieve SVR12. -The characteristics that were significantly more common in non-responders was HCV genotype 3 (OR 1.9), Child Pugh class B/C, bilirubin levels >1.5mg/dl (OR 1.8), and platelets ≤120,000/mm^3 (OR	-In this real-life study, the overall failure rate in those with advanced liver disease was 3.6%, which was similar to or lower than those reported in other clinical trials. Interim results

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
		patients who were retreated with a 2nd DAA regimen during Jan 2015-June 2016)	June 2016 -Patients could have advanced and progressive liver disease, severe extra-hepatic HCV manifestations and those who had undergone orthotropic liver transplant	encephalopathy, SBP, varices, esophageal variceal bleeding, hepatocellular carcinoma [HCC] development)	2.6). - A regimen of SOF+RBV compared those with 2 DAAs were more frequently associated with non-responders; it was associated with a failure rate of 9.6%, and SOF+SIM± RBV had a rate of 5.2%. -Of the 139 patients who did not achieve SVR, 51.8% (72) were retreated with a second DAA regimen ± RBV and also had liver cirrhosis. 52.8% were retreated with SOF/DCV and 37.5% with SOF/LDV. SVR was achieved in 95.8% of these patients (94.7% of SOF/DCV, 96.3% of SOF/LDV patients). -Following SVR, improvements in Child-Pugh class was observed in 23.6% of those with decompensated liver disease, the median MELD score after retreatment significantly improved from 15 to 10 ($p<0.001$) and did not change in the other retreated patients. -Both ascites and encephalopathy	demonstrated that those who failed treatment had worsening of liver disease but was reversed through successful treatment in the majority of patients.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					numerically increased after treatment failure but decreased after SVR12. HCC was seen in 13.8% (16/116) at baseline and in an additional 4 of 56 (7.1%) patients at SVR12 after retreatment who were HCC-free at baseline.	
Isakov et al[285] 2017 **LOE-2**	Phase IIIb, open-label study LDV/SOF for 8 weeks	N=126 20 weeks	-Adults with chronic HCV infection who were treatment-naïve or SOF-experienced. Treatment-naïve patients were required to have genotype 1, no cirrhosis and with or without HIV-1 Exclusions: HBV co-infection, history of drug or alcohol abuse, malignancy, or prior transplantation	-Proportion of patients with SVR12 -Other outcomes: resistance-associated substitution (RAS), AEs, and HIV virologic rebound	- 67 of 69 (97%) treatment-naïve, mono-infected and 57 of 59 (96.6%) treatment-naïve, co-infected patients achieved SVR12 with no on-treatment failures. -There were 3 patients with baseline NS5A RASs and 34 genotype 1b-L159F NS5B RAS at baseline. All with baseline RASs achieved SVR and no patients who relapsed had RASs at baseline or time of virologic failure. -28% and 29% of mono-infected and co-infected patients experienced at least 1 AE. The most common treatment associated AE was headache for both groups. There were no grade 4 or serious AEs reported and no deaths for either group. No patients discontinued or modified	-The authors concluded that non-cirrhotic, treatment-naïve patients with genotype 1 HCV mono-infection and HCV/HIV-1 co-infection achieved high rates of SVR12 with 8 weeks of treatment with LDV/SOF. **CHC Comments:** -This was a small study population, who were mostly white patients (n=125). The co-infected patient population was younger than the

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					drug therapy. -For HIV co-infected patients, there were no renal events and no clinically significant changes in CD4 counts from baseline. No patients experienced an HIV virologic rebound.	mono-infected patients and were more likely to be infected with genotype 1a infection.
Zeuzem et al[287] 2018 **LOE-2**	Two phase 3, randomized, open-label, multicenter trials 1: GLE/PIB for 8 vs. 12 weeks (genotype 1) 2: GLE/PIB Vs SOF/DCV x 12 weeks or GLE/PIB x 8 weeks (genotype 3)	N=1,208 20-24 weeks	-Patients 18+ years old without cirrhosis with HCV genotype 1 or 3 infection with HCV RNA >1000 IU/mL -Genotype 1 patients could have HIV-1 coinfection and could have received previous HCV treatment -Genotype 3 patients had to be HCV treatment naive	-Rate of SVR 12 weeks after the end of treatment -Virologic failure during treatment (breakthrough) -Post-treatment relapse	Genotype 1 SVR12 -GLE/PIB x 8 wks: 99.1% -GLE/PIB x 12 wks: 99.7% Genotype 3 SVR12 -GLE/PIB x 8 wks: 95% -GLE/PIB x 12 wks: 95% -SOF/DCV x 12 wks: 97% Genotype 1 breakthrough -GLE/PIB x 8 wks: <1% -GLE/PIB x 12 wks: 0 Genotype 3 breakthrough -GLE/PIB x 8 wks: 1% -GLE/PIB x 12 wks: <1% -SOF/DCV x 12 wks: 0 Genotype 1 relapse: -GLE/PIB x 8 wks: 0 -GLE/PIB x 12 wks: 0 Genotype 3 relapse:	-GLE/PIB for either 8 or 12 weeks achieved high rates of SVR among patients with HCV genotype 1 or 3 infection who did not have cirrhosis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			Exclusions: HBV co-infection, more than one HCV genotype		-GLE/PIB x 8 wks: 3% -GLE/PIB x 12 wks: 1% -SOF/DCV x 12 wks: 1%	
Ferreira et al[289] 2018 **LOE-2**	Retrospective, observational, multicenter study SOF/DCV ± RBV Vs SOF/SMV ± RBV with other DAA options included	N=296 24-36 weeks	-Patients 18+ years old with chronic HCV regardless of genotype, fibrosis stage, or prior treatment -Data were retrieved from 6 centers in Southern Brazil	-SVR 12+ weeks after the end of treatment (SVR12) -Rapid virologic response (RVR) after 4 weeks of therapy -EOT at treatment completion	-Overall SVR12 rates were approximately 91.6% -Genotype 1 SOF/DCV: 95% -Genotpe 1 SOF/SMV: 92% -Genotype 3 SOF/DCV: 84% -RVR was obtained by 94% of patients treated with SOF/DCV and 89% of patients treated with SOF/SMV -EOT was achieved by 90% of patients treated with SOF/DCV and 100% of patients treated with SOF/SMV	-Second generation DAAs are effective for the treatment of chronic HCV in patients in Southern Brazil. Genotype 3 appears to be the most difficult to treat, but current SVR rates with second generation DAAs were higher than with previous therapies. Apart from the difference between genotypes, and a difference between RVR rates, there were no other statistically

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
						significant factors associated with SVR. **CHC comments:** Results limited due to relatively small sample size and variation in treatment regimens.
Pott-Junior et al[290] 2018 **LOE-2**	Randomized, open-label, single-center noninferiority phase 4 study SOF/DCV Vs SOF/SMV for 12 weeks	N=125 24 weeks	-Patients 18+ years old with chronic HCV genotype 1 with cirrhosis-treatment naïve or pegylated interferon experienced, HCV RNA >10,000 IU/mL -Exclusions: chronic liver disease unrelated to HCV, coinfection with HIV of HBV, previous treatment with	-SVR at 12 weeks after treatment -RVR at week 4 -EOT at 12 weeks -Adverse effects	-SVR12 -SOF/DCV: 100% -SOF/SMV: 93.3% (p=0.108) -RVR at 4 weeks -SOF/DCV: 83% -SOF/SMV: 70% (p=0.083) -EOT at 12 weeks -SOF/DCV: 100% -SOF/SMV: 100% -The most common adverse effects were fatigue (25.6%), headache (21.6%), and mood swings (19.2%)	- The SVR rate of SOF/DCV was higher than that of SOF/SMV and despite no statistically significant difference, the noninferiority of SOF/SMV to SOF/DCV could not be established because the difference in efficacy was clinically significant. **CHC comments:** Results may be limited due to small

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			DAA			sample size.
Rockstroh et al[292] 2018 **LOE-2**	Non-randomized, open-label, phase 3, multicenter study GLE/PIB in patients with HCV/HIV-1 coinfection for 8 weeks (noncirrhotic) or 12 weeks (cirrhotic)	N=153 20-24 weeks	-Patients 18+ years old with a BMI >18 with HIV-1/HCV coinfection with or without cirrhosis -Patients with genotype 3 HCV could not have received previous HCV treatment, all other patients could be treatment-naïve or experienced -Patients could be ART naïve with a CD4+ count ≥ 500 or ART stable with CD4+ ≥ 200 -Exclusions: Positive HBV screen, >1 HCV	-SVR at 12 weeks after treatment -On-treatment virologic failure -Post-treatment relapse	-SVR at 12 weeks after treatment: 98% -without cirrhosis: 100% -with cirrhosis: 93% -On-treatment virologic failure: 1 patient (genotype 3 + cirrhosis) -Post-treatment relapse: None	-Glecaprevir/pibrentasvir for 8 weeks in noncirrhotic and 12 weeks in cirrhotic patients was highly efficacious and well tolerated in patients with HCV/HIV-1 coninfection, regardless of baseline HCV load or prior treatment with interferon of sofosbuvir. All patients treated with ART maintained HIV-1 suuppression (<200 copies/mL) during treatment. **CHC comments:** Results may be limited due to small sample size; however, the study group was a

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			genotype, ALT or AST >10x ULN, albumin <3, CrCl <50, PLT <60,000 or 90,000 with or without cirrhosis, respectively			subgroub and was inclusive of most patients.
Wei et al[293] 2018 **LOE-2**	Multicenter, open-label, phase 3b study SOF + RBV ± peginterferon for 12-24 weeks	N=389 24-36 weeks	-Patients 18+ years old with HCV genotype 1,2,3 or 6 and HCV RNA levels $\geq 10^4$ IU/mL -Patients were either treatment naïve or experienced -Up to 20% of patients could have compensated cirrhosis	-SVR at 12 weeks after treatment -Adverse events leading to permanent discontinuation of study drug(s) -SVR at 4 weeks after treatment -Relapse	-Genotype 1 -SOF/peg-IFN/RBV x 12 wks -SVR12: 94% -SVR4: 95% -Relapse: 6% -SOF/RBV x 24 wks -SVR12: 95% -SVR4: 95% -Relapse: 5% -Genotype 6 -SOF/peg-IFN/RBV x 12 wks -SVR12: 97% -SVR4: 100% -Relapse: 3% -SOF/RBV x 24 wks -SVR12: 100% -SVR4: 100% -Relapse: 0% -Genotype 2 -SOF/RBV x 12 wks	-Sofosbuvir-based regimens were highly effective and safe in Chinese patients with HCV genotype 1, 2, 3, or 6. This suggests that sofosbuvir could serve as the backbone for HCV treatment in China irrespective of genotype.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-SVR12: 92% -SVR4: 94% -Relapse: 6% -Genotype 3 -SOF/RBV x 24 wks -SVR12: 95% -SVR4: 98% -Relapse: 5% -10 patients (3%) experienced serious adverse events, 3 (<1%) discontinued treatment because of adverse events. -Most common AEs were increased reticulocyte count, pyrexia, and anemia.	
Agarwal et al[294] 2018 **LOE-2**	Phase II open-label study SOF/VEL for 12 weeks in liver transplant recipients	N=79 24 weeks	-Patients 18+ years old with genotype 1-4 HCV who received a liver or liver-kidney transplant at least 3 months prior to study -Patients without cirrhosis or with	-SVR at 12 weeks after treatment -SVR at 4 weeks after treatment -Discontinuation due to adverse events -Adverse events	SVR12: -Total: 96% -GT1a: 93% -GT1b: 95% -GT1: 95% -GT2: 100% -GT3: 97% -GT4: 100% SVR4: 97% overall -Discontinuation due to adverse events: 1 patient with a history of	-Sofosbuvir/velpatasvir was well tolerated and highly effective in genotype 1-4 HCV-infected liver transplant recipients. **CHC comments:** Results may be

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			compensated cirrhosis were eligible		diabetes discontinued SOF/VEL due to hyperglycemia -Most common adverse events: headache (24%), fatigue (20%), and cough (10%)	limited due to small sample size; however, the study group was a subgroub and was inclusive of most patients.
Kim et al[295] 2018 **LOE-2**	Retrospective multi-institutional study SOF + RBV in genotype 2 HCV patients	N=163 24-28 weeks	-Patients 18+ years old with HCV genotype 2 infection with or without cirrhosis from 8 hospitals in the Daejeon-Chungcheong area of South Korea were analyzed -Patients were excluded if they did not reach text for SVR12, were not followed up to end of treatment, or if they expired due to non-liver disease	-Virologic response at 4, 8, 12 weeks during and 12 weeks after treatment -Adverse events	-Virologic response at 4 weeks: 97.5% -Virologic response at 8 weeks: 99.1% -Virologic response at 12 weeks: 99.3% -SVR12: 98.8% -Most common adverse events: anemia (15.3%), dizziness (8%), fatigue (3.7%) -During treatment, 11% of patients had to reduce dose of ribavirin because of anemia and 1 patient stopped treatment due to severe anemia.	-A 12-16-week treatment with sofosbuvir plus ribavirin is effective and well tolerated in Korean patients with chronic HCV genotype 2 infection.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Butt et al[296] 2018 **LOE-2**	Retrospective, multi-center observational study SOF/LDV Vs PrOD in patients with CKD	N= 13,663 on SOF/LDV N=3961 on PrOD	-Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) was used for data collection -Patients who received sofosbuvir/ledipasvir and paritaprevir/ritonavir/ ombitasvir + dasabuvir regimens were included -Exclusions: HIV coinfection, lack of genotype information or eGFR at baseline and 12 or more weeks after treatment	-SVR at 12 weeks after treatment -Progression of renal disease on and up to 12 weeks after treatment by CKD stage -Treatment completion rates -Hematologic toxicity	-Patients with CKD stage 1-2 -SVR12: -SOF/LDV: 96.4% -SOF/LDV + RBV: 94.7% -PrOD: 98.5% -PrOD + RBV: 96.9% -Completed therapy: -SOF/LDV: 64.5% -SOF/LDV + RBV: 74.1% -PrOD: 85.8% -PrOD + RBV: 70.8% - >10 mL/min/1.73 m^2 eGFR decline -SOF/LDV: 33.1% -SOF/LDV + RBV: 37.8% -PrOD: 30.1% -PrOD + RBV: 33.2% -Patients with CKD stage 3 -SVR12: -SOF/LDV: 97% -SOF/LDV + RBV: 97.1% -PrOD: 96% -PrOD + RBV: 95.3% -Completed therapy: -SOF/LDV: 68.9% -SOF/LDV + RBV: 77.9% -PrOD: 78.9% -PrOD + RBV: 69.8%	Sofosbuvir/ledipasvir and paritaprevir/ritonavir/ ombitasvir + dasabuvir achieved high SVR rates in patients with CKD. -Treatment completion rates were lower than expected. A decline in eGFR and development of anemia were seen in many patients, but clinical implications remain unclear.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					- >10 mL/min/1.73 m^2 eGFR decline -SOF/LDV: 16.5% -SOF/LDV + RBV: 15.9% -PrOD: 17.5% -PrOD + RBV: 14.1% -Patients with CKD stage 4-5 -SVR12: -SOF/LDV: 94% -SOF/LDV + RBV: 100% -PrOD: 100% -PrOD + RBV: 89.13% -Completed therapy: -SOF/LDV: 68.2% -SOF/LDV + RBV: 83.3% -PrOD: 69.1% -PrOD + RBV:66.2% - >10 mL/min/1.73 m^2 eGFR decline -SOF/LDV: 6.5% -SOF/LDV + RBV: 3.3% -PrOD: 1.8% -PrOD + RBV: 0 -Incidence of grade ¾ anemia was significantly higher in patients with baseline stage 4-5 CKD for	

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					both treatment regimens	
Mehta et al[297] 2018 **LOE-2**	Single center, prospective, observational study SOF/LDV or SOF/DCV with genotypes 1, 3, and 4	N=648 24-36 weeks	-Patients with chronic HCV genotypes 1, 3, and 4 with or without cirrhosis who were treated with DAAs -Patients with HBV or HIV coinfections were included -Exclusions: CKD, advanced liver disease, portal vein thrombosis, HCC	-RVR at 4 weeks -ETR (end of treatment response) at 12 or 24 weeks -SVR at 12 weeks -Non-response -Breakthrough -Virologic relapse -Adverse effects	-RVR at 4 weeks: 94.4% -ETR at 12 or 24 weeks: 98.7% -SVR at 12 weeks -Overall: 88.1% -Genotype 1: 96.8% -Genotype 3: 85.2% -Genotype 4: 93.5% -Non-response: 6 patients (0.93%) -Breakthrough: 2 patients (0.3%) -Virologic relapse: 10 patients (1.5%) -Most common adverse effects: fatigue and anemia	-Direct acting antiviral therapy for HCV genotypes 1, 3, and 4 achieves high SVR rates in all patients, including those with cirrhosis and previous non-responders.
Shiha et al[298] 2018 **LOE-2**	Open-label, multicenter, phase III study SOF/LDV ± RBV for 8-12 weeks in HCV genotype 4	N=255 20-24 weeks	-Patients 18+ years old with chronic HCV genotype 4 with or without compensated cirrhosis -Patients could be treatment	-SVR at 4 weeks after treatment -SVR at 12 weeks after treatment -On-treatment virologic failure -Post-treatment	-Treatment naïve -SOF/LDV 8 weeks -SVR4: 95% -SVR12: 95% -Failure: 0 -Relapse: 5% -SOF/LDV + RBV x 8 weeks -SVR4: 95% -SVR12: 90% -Failure: 2%	-Among non-cirrhotic treatment-naive patients with HCV genotype 4, 8 weeks of ledipasvir/ sofosbuvir ± ribavirin was highly effective. 12

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			naïve or treatment experienced eith interferon, SOF, or SOF/LDV Exclusions: hepatic decom-pensation, HBV or HIV coinfection, contraindications to RBV	relapse -Adverse events leading to permanent discontinuation of study drug	-Relapse: 7% -SOF/LDV x 12 weeks -SVR4: 98% -SVR12: 98% -Failure: 0 -Relapse: 2% -SOF/LDV + RBV x 12 weeks -SVR4: 98% -SVR12: 98% -Failure: 0 -Relapse: 0 -SOF or SOF/LDV experienced -SOF/LDV + RBV x 12 weeks -SVR4: 100% -SVR12: 100% -Failure: 0 -Relapse: 0 -Interferon experienced -SOF/LDV x 12 weeks -SVR4: 100% -SVR12: 94% -Failure: 0 -Relapse:3% -SOF/LDV + RBV x 12 weeks -SVR4: 100% -SVR12: 100% -Failure: 0 -Relapse: 0	weeks of ledipasvir/ sofosbuvir ± ribavirin was highly effective regardless of presence of cirrhosis or prior treatment experience, including previous treatment with sofosbuvir or ledipasvir/ sofosbuvir.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-1 patient discontinued treatment due to leg amputation following a road traffic accident	
Tsuji et al [299] 2018 **LOE-2**	Retrospective analysis of a prospective, nationwide, multicenter registry SOF/LDV for 12 weeks in HCV genotype1	N= 1461 24 weeks	-Cohort assembled by the Japanese Red Cross Liver Study Group -Patients with HCV genotype 1 infection for received SOF/LDV without RBV for 12 weeks -Exclusions: decompensated cirrhosis, eGFR <30, DCV/ASV treatment experienced	-SVR at 12 weeks after treatment -Incidence of adverse events -Serum markers of hepatocellular carcinoma	-Overall SVR12: 98.4% -SVR12 in patients with cirrhosis or NS5A RASs: 93% -Adverse events were rare and included headache (0.6%), tiredness (0.5%), and diarrhea (0.3%) - In patients with SVR, the levels of alpha-fetoprotein (AFP), AFP-L3, and Mac-2 binding protein glycosylation isomer (M2BPGi) (HCC biomarkers) decreased from baseline to end of treatment (from 13.4 to 6.0 ng/mL p<0.0001; from 2.2 to 1.5, p<0.005; and from 3.6 to 2.0, p<0.0001; respectively)	-SOF/LDV is highly effective and safe in Japanese patients with HCV genotype 1, even in the presence of cirrhosis or NS5A RASs. Patients with SVR may have a lower risk of HCC.
Uojima et al[300] 2018 **LOE- 2**	Multicenter, prospective study ombitasvir/paritaprevir /ritonavir	N =70 12 weeks	-Elderly patients > 65 years old, Chronic HCV genotype 1b infection for at	-SVR12 -Secondary Endpoint: Pharmacological effects and	-Overall SVR12: 95.7% -SVR12 for patients > 65 in age was 94% compared to 100% in younger patients, but no	-Overall, it was noted that combination therapy of OBV/PTV/ritonavir

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			least 6 months Plasma HCV RNA > 2IU/mL	tolerability of the combination therapy	significant difference was found -There was a decrease of 81.4% in HCV-RNA levels after 4 weeks of treatment -Virological failure: 4.3% of patients (all > 65 years of age and eGFR < 60) - The SVR rate in patients with poor renal function was high with little difference in those patients with normal renal function. -Reported in 16 patients (22.8%) Discontinuation of therapy occurred in 6 patients due to AEs including: edema, acute kidney injury, fatigue, and hypertension. With edema being the most commonly reported AE. -Change or discontinuation of concomitant drugs due to drug interactions was an independent risk factor for AEs (P = 0.15).	was highly efficacious in elderly patients with HCV genotype 1b infection. There was not a reported difference in SVR based on age.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Takehara et al[301] 2019 LOE- 2	Open label multicenter phase III Trial sofosbuvir-velpatasvir +/- ribavirin	N =102 12 weeks	-Adults > 20 in Japan years old with chronic HCV infection Child-Pugh-Turcotte (CPT) score 7-12, inclusive	-SVR12 at 12 weeks post- treatment. -Significant change from baseline in CPT & MELD score at 12 weeks post treatment. Safety was measured as discontinuation of study drugs due to AEs.	-SVR12: 92% in each treatment group (sofosbuvir-velpatasvir + ribavirin and sofosbuvir-velpatasvir) which was statistically superior compared with the spontaneous clearance rate of 1% ($p<0.001$). -By genotype SVR12 rates were increased in the patients with genotype 1 or 2 regardless of the duration of treatment they received. -In baseline CPT patients SVR12 rates were higher in those with class B cirrhosis (95% without and 97% with ribavirin) as compared with CPT class C (80% without and 70% with ribavirin). -In patients who achieved SVR12, 26% had improvement in CPT class from baseline to week 12. -8% (4/51) of patients did not achieve SVR12 in the sofosbuvir-velpatasvir + ribavirin group. Of these 4, 2 relapsed & 2 discontinued treatment due to AEs.	-Overall sofosbuvir-velpatasvir x 12 weeks was highly efficacious and generally safe in patients with decompensated cirrhosis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-Overall, those patients who were treated with sofosbuvir-velpatasvir + ribavirin experienced more AEs (86%) vs 69% in those treated with sofosbuvir-velpatasvir.	
Hunyady et al[302] 2018 **LOE- 2**	Retrospective observational study ombitasvir/paritaprevir /ritonavir + dasabuvir + ribavirin in genotype 1	N = 127 24 weeks	-Patients who failed boceprevir or telaprevir one year prior.	-SVR12, SVR24 & SVR12/24 -Safety adverse events that resulted in discontinuation or dose reductions	-Of the patients observed, 87.4% had cirrhosis SVR12: 97.6% SVR24: 98.8% SVR12/24: 96.1% -Grade 1 anemia was reported in 24 patients, with 9 requiring RBV dose reduction (by 200-400mg). -No early discontinuation of drugs due to SAEs was reported.	-It was concluded that 12 weeks of therapy with ombitasvir/ paritaprevir/ ritonavir + dasabuvir + ribavirin was effective in patients who failed boceprevir or telaprevir one year prior (even in the presence of cirrhosis)
Liu et al[303] 2018 **LOE- 2**	Retrospective single center study SOF/LDV +/- RBV	N = 273 24 weeks	-Adults >20 years old Had chronic HCV + quantifiable serum HCV RNA > 6 months	-Evaluable population (EP) which looked at the SVR12 for patients who received at least 1 dose of treatment -Per-Protocol	-At week 4 HCV RNA was undetectable in 80.2% of patients -All patients with available HCV RNA data had undetectable HCV RNA at the end of treatment -Overall SVR12 Rate: 96.7% by EP	-The authors concluded that SOF/LDV +/- RBV for 8-24 weeks is well tolerated and effective in patients with HCV-1 infection.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
				population (PP) which looked at SVR12 by excluding non-SVR12 patients -Patients who discontinued therapy due to AEs	& 97.5% by PP (95% CI 94.8-98.8%) -2.6% of patients relapsed & 0.7% were lost to follow up and therefore SVR12 was not achieved. -99.6% of patients completed the full course of scheduled treatment. -Common AE included fatigue (27.1%), headache (20.5%), and nausea (17.9%). -Rates of patients who discontinued therapy due to serious AEs were 0.4% and 4.4% for EP and PP, respectively.	
Tamai H et al[304] 2018 **LOE- 2**	Multicenter, Post-marketing, Prospective Cohort Study SOF/LDV	N =507 12 weeks	-Infected with genotype 1 eGFR > 30mL/min	-SVR12 at the end of therapy -AEs monitored every 2 weeks; labs included CBC and LFTs and this led to determination of therapy discontinuation	-Overall SVR12 was 98%; with no significant difference between age groups. -2% of patients did not achieveSVR12. High body weight, discontinuation of therapy, and N5SA RASs were significantly associated with non-SVR.	-The authors concluded that SOF/LDV was safe and effective in patients, even those ≥75 years old.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-Rate of patients who discontinued therapy due to AEs was 0.8%, with the most frequent AE being elevation of uric acid levels.	
Izumi N et al[305] 2018 LOE- 2	Phase III, multicenter, open label study sofosbuvir-velpatasvir + ribavirin	N =117 12 or 24 weeks	-Adults >20 years old with plasma HCV RNA > 10IU/mL + chronic genotype 1 or 2 HCV that failed to achieve SVR with a DAA regimen lasting > 4 weeks	-SVR12 -Primary Safety endpoint was discontinuation of study drugs due to adverse events	-Overall SVR12 rates were higher with 24 weeks vs 12 weeks of treatment. In the 12- and 24-week treatment groups 82% vs. 97% achieved SVR12, respectively. -HCV genotype 1 SVR12 rates were 85% with 12 weeks and 98% with 24 weeks ($p<0.001$ for 12 weeks and for 24 weeks compared to historical control rate of 50%). -HCV genotype 2 SVR12 rates were 80% for 12 weeks and 92% for 24 weeks. -The difference in SVR12 rates for the treatment groups overall was statistically significant (24 weeks vs 12 weeks for all patients, $p=0.023$). However, the differences in SVR12 rates by genotype for the treatment groups were not statistically significant ($p=0.0548$ for GT1 & $p=0.4511$ for GT2)	-The authors concluded that sofosbuvir-velpatasvir plus ribavirin is highly effective and well tolerated in Japanese patients who previously failed a DAA regimen

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-For those with NS5A RASs at baseline 85% reached SVR12 and 96% reached SVR24 -Safety endpoint: 81% (12 weeks) and 75% (24 weeks) of patients experienced AEs; the most common being viral upper respiratory tract infection (28%), anemia (23%) and headache (11%). -3 patients had AEs that led to discontinuation of treatment; 10 patients had dose reductions due to AEs.	
Janczewska et al[306] 2018 **LOE- 2**	Multicenter Cohort Study paritaprevir/ritonavir/ ombitasvir + dasabuvir (PrODR) & ledipasvir/sofosbuvir (LSR)	N = 335 24 weeks	-Patients who failed prior triple IFN-based therapies with first generation protease inhibitors (boceprevir (BOC) or telaprevir (TVR))	-SVR (at least 12 weeks after treatment completion) in the boceprevir (BOC) → ledipasvir/sofosbuvir -SVR in the boceprevir (BOC) → PrODR -SVR in the telaprevir (TVR) → LSR or	-SVR = 98% & 99% (intent to treat & modified intent to treat groups) for BOC → LSR -SVR = 100% (both intent to treat & modified intent to treat groups) for BOC → PrODR -SVR = 96% & 98% (intent to treat & modified intent to treat groups) for TVR→ LSR -SVR = 97% & 99% (intent to treat	-Efficacy and safety of PrODR and LSR is comparable in BOC or TVR experienced patients.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
				PrODR groups -AEs that resulted in discontinuation or dose reduction of treatment	& modified intent to treat groups) for TVR → PrODR -All patients that discontinued therapy (5 discontinued due to AEs) reached SVR despite reduced duration of treatment. -1 BOC and 2 TVR patients failed to achieve SVR -1 patient in the TVR group had a serious AE that resulted in discontinuation during week 9.	
Asselah et al[307] 2019 **LOE- 2**	Open Label, single arm, multicentered phase 3b trial glecaprevir/ pibrentasvir	N =84 12 weeks	-Adults > 18 years old with chronic HCV genotype 5 or 6 infection Without cirrhosis or with compensated cirrhosis	-SVR12 assessed by HCV genotype across treatment durations or cirrhosis status -Proportion of patients with on-treatment virological failure or post treatment relapse -Safety	-Overall SVR12 was 97.6% (95% CI 94.4-100) -SVR12 for those with genotype 5 was 95.7% (95% CI 87.3-100) -SVR12 for those with genotype 6 was 98.4% (95% CI 95.2-100) -Most patients reached viral suppression by week 4 of treatment (95.2%). -1 patient with HCV genotype 6f infection + compensated cirrhosis ended up with on-treatment virological failure at week 12 of	-Glecaprevir/ pibrentasvir treatment resulted in overall high rates of SVR12 and was well tolerated in patients with HCV genotype 5 or 6 infection even in those with compensated cirrhosis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					treatment. SVR12 for patients with compensated cirrhosis was 89%. -Mostly mild AEs reported (46 events in total) with the most common being fatigue & headache. None of these led to dose reduction or discontinuation.	
Takeuchi et al[308] 2018 **LOE- 2**	Retrospective cohort study elbasvir/grazoprevir (EBR/GZR)	N = 147 12 weeks	-Patients from Japan had chronic HCV genotype 1b infection (without cirrhosis or hepatocellular carcinoma)	-Overall SVR12 -Treatment efficacy based off CKD stage -SVR12 in patients with CKD all stages -Retreatment with patients that relapsed	-Overall SVR12: 94% Naïve to DAA treatment SVR12: 97% Failure to respond to prior DAA SVR12: 58% -CKD stage 1 was the only stage where patients had significant changes in eGFR during treatment (p= 0.010). -CKD stage 1-2 SVR12: 96% CKD stage 3 SVR12: 98% CKD stage 4-5 SVR 100% -Relapsers of first DAAs (excluding ledipasvir and sofosbuvir) achieved SVR12. -3 patients with double mutant NS5A-L31/Y93 did not achieve	-Overall if patients have the HCV genotype 1b EBR/GZR is effective even in those with CKD stage 4-5.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					SVR.	
El-Khayat et al[309] 2019 LOE- 2	Prospective cross-sectional study sofosbuvir/ledipasvir (SOF/LVD)	N= 157 12 weeks	-Age 12-17 Weight was at least 35kg Chronic HCV infection irregardless of fibrosis stage	-SVR12 -Relapse at any time of the study -Safety	-Overall SVR12 for all treated patients was 98% (95% CI 96-100) -For 12-week treatment group SVR12 was 97.6% (95% CI 96-101) -For 8-week treatment group SVR12 was 98.6% (95% CI 93-101) -Adherence to treatment was 100%. -For 8-week treatment group HCV RNA clearance at week 4 = 63% -For 12-week treatment group HCV RNA clearance at week 4 = 58%. -No serious AEs were reported that led to discontinuation of therapy. 7.6% of patients experienced AEs.	-Looking at adolescent HCV infected patients, SVR12 was high in all the treated patients, with 100% adherence to treatment throughout the study. Overall SOF LVD in genotype 4 patients is equally safe and effective for 8 weeks or 12 weeks.
Murray et al[310] 2018 LOE- 2	Phase 2 multicenter, open label study ledipasvir/sofosbuvir +/- ribavirin	N =92 24 weeks	-6 to < 12 years old, Chronic HCV with genotype 1,3,4,5, or 6; Plasma HCV	-SVR12 was the primary efficacy endpoint -Safety	-Overall SVR12 = 99% SVR based on specific genotype: -12 weeks: LVD/SOF Genotype 1: 99% Genotype 4: 100%	-Ledipasvir/ sofosbuvir +/- ribavirin for 12 or 24 weeks was shown to be effective in

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			RNA levels > 10^4 IU/mL, Absolute neutrophils > 1500mm^3 and Hemoglobin > 11g/dL (female); > 12 (male)	-Pharmacokinetics lead-in cohort	-24 weeks: LVD/SOF Genotype 1: 100% -24 weeks: LVD/SOF + RBV Genotype 3: 100% -1 patient experienced relapse; 8-year-old, genotype 1a, + for cirrhosis, received LVD/SOF and has virologic relapse 4 weeks after completing the 12 weeks of treatment. -AEs reported: headache (18%), pyrexia (17%), abdominal pain/fatigue/vomiting/cough (15%). -No patients discontinued treatment because of AEs. -PK results: 2 patients that received an adult dose were within the PK equivalence boundaries of 50-200% when they were compared to adults from other studies.	adolescents < 12 years of age with genotypes 1, 3 & 4 HCV infection.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Kwon J et al[311] 2019 **LOE- 2**	Retrospective Multi-center Cohort daclatasvir + asunaprevir (DCV + ASV) x 24 weeks or daclatasvir + sofosbuvir (DCV + SOF) x 12 weeks or sofosbuvir/ledipasvir (SOF/LDV) x 12 weeks	N = 590	->18 years old, CHC-1b Hep C + detectable HCV RNA for at least 6 months Nonresponsive to previous IFN therapy/ relapsed.	-SVR12 -HCC recurrence or de novo HCC occurrence during therapy or 1-year post DAA therapy.	-DCV + ASV x 24 weeks: 518 patients; SVR12: 94% -SOF/LDV + ribavirin x 12 weeks: 61 patients; SVR12: 98.2% -SOF + DCV + ribavirin x 12 weeks: 11 patients; SVR12: 100% -SVR12 was significantly lower in the RAV (+) group compared to the RAV (-) group and indeterminate group (26.6% vs 95% and 93.3%; p=0.000). -The group with high HCV RNA levels (>800,000) reported lower SVR12 rates compared to those with lower levels (p=0.002) -Those treated with DCV +ASV and renal impairment had consistent SVR12 rates compared to no renal impairment (87.5% vs 93.9%; p=.393). No difference in SVR12 based on cirrhosis, age, or prior treatment experience. -1 year follow up: 2.6% of patients developed de novo HCC 17.8% had recurrence of previous	-This study found that optimizing the choice of treatment based on RAV test resulted in high SVR rates. Additionally, the study concluded that HCC monitoring in patients with cirrhosis is essential.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					HCC; all of these patients did achieve SVR12. HCC was more frequent in patients with cirrhosis (p=0.000) -10% of patients discontinued therapy due to drug cost/non-medical reasons. -6.7% had symptomatic AEs (fatigue/weakness). 24 patients in the DCV +ASV group developed elevated aminotransferases and ribavirin-induced anemia was found in 13 patients in SOF tx groups.	
D'Ambrosio R et al[312] 2018 **LOE- 2**	Retrospective longitudinal multicenter cohort study glecaprevir/ pibrentasvir	N = 723 12 weeks	-Italian patients with HCV that were on therapy from Oct 2017 to Jan 2018.	-Rates of SVR12 -Rates of treatment discontinuation and deaths due to AEs related to treatment -Incidence of AEs -Rate of week 4 response -Rate of EOT response	-Overall SVR12 = 94% (ITT) and 99.3% (PP) -SVR rates were lower in males (p=0.002) and genotype 3 patients treated for 8 weeks (p=0.046) and these were determined to be independent predictors of treatment failure. -73% of patients had on treatment virological response at week 4, independently of treatment duration. HCV-RNA was <LLoQ in 26% and undetectable in 48% in	-Glecaprevir/ pibrentasvir for 8 or 12 weeks is highly effective and safe in the real-world setting.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					this group. EOT response was achieved by 97% of patients with no difference in duration of weeks (P=1.0). -5 patients had virological relapse and failed therapy. -8.3% of patients reported treatment related AEs. Commonly reported: pruritus (2.5%), fatigue (2%), nausea (1.5%), and headache (1.0%). -4 patients discontinued therapy due to AE; all having genotype 2 or 3 and cirrhosis.	
Belperio et al[313] 2018 **LOE- 2**	Observational intent-to-treat cohort analysis DCV+ SOF ± RBV and VEL/SOF ± RBV	N = 2,939 patients with HCV genotype 2 and 2,824 patients with genotype 3 24 weeks	-Patients infected with HCV genotype 2 and 3 who started VA-prescribed DCV + SOF ± RBV or VEL/SOF ± RBV Exclusion: Patients were excluded if their baseline HCV RNA were ≤	-SVR	-In patients with HCV genotype 2, SVR rate achieved was 93.9%. SVR rates did not differ between groups who received DCV + SOF (94.5%) and VEL/SOF (94.4%) or between patients who received DCV + SOF + RBV (88.1%) and VEL/SOF + RBV (89.5%) (P=1.00). -In patients with HCV genotype 3, SVR rate achieved was 90.2% and the rates did not differ between DCV + SOF (90.8%) and VEL/SOF (92.0%) or between DCV + SOF +	-DCV + SOF± RBV and VEL/SOF ± RBV produced similar SVR rates in both GT2 and GT3. This showed that both medication regimens are effective in treating infections in GT2 and GT3.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			1,000 IU/ml or they had undergone liver transplant		RBV (88.1%) and VEL/SOF + RBV (86.4%) (P=0.51). -In patients with HCV genotype 3, significant predictors of reduced odds of SVR were prior HCV treatment experience (P <0.001) and a history of decompensated liver disease (p=0.04).	
Takeda et al[314] 2018 **LOE- 2**	Retrospective cohort study daclatasvir/ asunaprevir (DCV/ASV) sofosbuvir/ ledipasvir (SOF/LDV) ombitasvir/paritaprevir /ritonavir (OBV/PTV/r) elbasvir/grazoprevir (EBR/GZR)	N = 287 24 weeks	-Patients with chronic hepatitis, with HCV genotype 1b, previous IFN therapy. Exclusion: Pregnancy, coinfection with another virus, history of clinical hepatic de-compensation or the use of immunosuppressants.	-Rapid virological response (RVR) at week 4, end of treatment (ETR) at week 12, sustained virologic response (SVR) at weeks 4 and 12 BDI-II questionnaire – to evaluate symptoms of depression	-In patients treated with DCV/ASV, the RVR, ETR, SVR4 and SVR12 were 76%, 92%, 93% and 92% respectively. -In patients treated with SOF/LDV, the RVR, ETR, SVR4 and SVR12 were 85%, 99%, 97%, and 98% respectively. -In patients treated with OBV/PTV/r, the RVR, ETR, SVR4 and SVR12 were 88%, 100%, 99% and 98% respectively. -In patients treated with EBV/GZR, the RVR, ETR, SVR4 and SVR12 were 85%, 100%, 100% and 100% respectively. -7 patients that had depression that were treated with DCV/ASV for 24 weeks had BDI-II scores that	-All 4 regimens produced very similar high efficacy in patients with HCV genotype 1 infection for 12 weeks. Treatment for 24 weeks had a temporary negative impact on mental health in patients with HCV infection. The authors concluded that the 12-week regimen of SOF/LDV or EBR/GZR can be safely used with high efficacy in patients with genotype-1 HCV

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					were increased at week 4 but lower scores at week 12 compared to pre-treatment, despite decline in serum HCV levels after medication initiation -BDI-II scores decreased significantly from baseline to the end of treatment with 12-week regimens of both SOF/LDV and EBR/GZR	infection, including those with depression.
Garcia-Pajares et al[315] 2019 **LOE-2**	Retrospective analysis sofosbuvir + daclatasvir simeprevir + sofosbuvir sofosbuvir + ledipasvir ombitasvir/paritaprevir /ritonavir	N = 40 F/U = 1 year	-Patients who underwent liver transplantation (LT) treated with direct-acting antivirals (DAAs), HCV genotype 1, genotype 3 and genotype 4.	-Liver function (MELD score), fibrosis stage, and clinical condition at start of treatment and at 6 and 12 months after SVR was achieved -Adverse events (AEs)	-The mean MELD score pretreatment was 10.78 compared to 8.46 at 1 year after treatment (p <0.5) -Improvement of fibrosis stage after SVR was also observed (from 14.81 kPa pretreatment to 9.07 kPa at 12 months posttreatment) -Significant improvements in control of ascites and hepatic encephalopathy were observed -AEs occurred in 29.5% of patients and were transient and mild; included peripheral edema, rash, insomnia, fatigue and transient increased aminotransferases	-Significant improvement in MELD score, fibrosis status as well as clinical complications were seen in patients with LT treated with DAAs. Further studies are needed to determine long-term benefits.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Kurniawan et al[316] 2018 **LOE-2**	Retrospective comparative study sofosbuvir-ribavirin (SOF + RBV) Vs sofosbuvir-daclatasvir (SOF + DCV) Patients received SOF 400mg and 1000mg RBV if body weight < 75kg OR 1200mg RBV if it was ≥ 75kg or 60mg DCV. Patients received DCV 90mg if there was co-infection w/ HIV	N = 309 12 weeks	-Indonesian patients with chronic HCV infection who were being treated with SOF	-SVR at 12 weeks after treatment	-99.3% of patients in the SOF + RBV group had no detectable viral load at the end of treatment and 99.4% of patients in the SOF + DCV group had no detectable viral load. -The patients in the SOF + DCV treatment group has a higher SVR 12 rate (98.2%) than that of the SOF + RBV treatment group (90.8%) at the end of treatment (P=0.034) -Patients with cirrhosis treated with SOF + RBV had SVR 12 rate of 84.4% compared to 94.7% in non-cirrhosis patients. -SOF+ DCV treatment group had SVR 12 rate of 100% in cirrhosis patients compared to 97.5% in non-cirrhosis patients. -5 patients w/ GT3 who received SOF + DCV and did not have cirrhosis achieved SVR12; 1 patient who had cirrhosis also achieved SVR12 after treatment with listed regimen.	-SOF + DCV treatment regimen showed a higher SVR rate compared to SOF + RBV. Despite this, both regimens achieved SVR 12 rates > 90% regardless of the presence or absence of cirrhosis and HCV genotype

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Liu et al[317] 2018 **LOE-1b**	Systematic review and meta-analysis, including 12 retrospective and 4 prospective studies PrOD, ASV/DCV, LDV/SOF, SMV/DCV w/w/o RBV and SMV/SOF w/w/o RBV	N = 885 patients in 16 studies 12 weeks	-Original studies which contained at least 5 patients, presented effectiveness of treatment of 2nd generation interferon-free DAA regimens for at least 12 weeks in LT recipients with HCV GT1 recurrence, SVR 12 after the end of treatment. Exclusion: Studies that enrolled LT recipients with coinfected with Hep A, B, D and E virus or HIV. Studies without reporting AEs.	-SVR12 - efficacy and tolerability of DAA treatment -Degree of liver fibrosis (METAVIR score)	-Overall, 91% of patients achieved SVR12. -SVR12 for LT patients was 93% (95% CI 0.89, 0.96) -Common adverse events included fever, fatigue and dizziness were seen in patients at an estimated rate of 37% -There was a trend for a higher SVR12 rate in patients with F0-F2 stages (97%) than patients with F3-F4 stages (85%) (P < 0.01) -There was no significant difference in SVR12 proportion between LT patients treated with or without RBV (P = 0.23)	-High rates of SVR12 suggest that DAA use was clinically effective in eliminating HCV genotype 1 infections recurrence post LT

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Poordad et al[318] 2018 **LOE-2**	Open-label, single-arm, multicenter, phase III study DCV+SOF+RBV	N = 78 24 weeks	-Patients ≥ 18 years with HCV GT3 infection, HCV RNA screening ≥ 10,000IULml, BMI between 18 and 40kg/m^2, compensated cirrhosis, treatment-naïve and coinfection with HCV and HIV-1 Exclusion – Patients with non-GT3 infection, mixed genotype infection	-Primary outcome – SVR12 Secondary outcome – achieving SVR12 in the presence and absence of baseline NS5A RASs, at post-treatment week 24 and on treatment safety	-Overall SVR12 was attained by 87% of patients. SVR12 rates were 93% in the treatment naïve group and 75% in treatment experienced group -In treatment-naive patients with or without RASs, 100% achieved SVR12. Among the treatment-experienced patients, only one had a baseline RAS and this patient did not achieve SVR12, but 95% without this RAS achieved SVR12. -9 patients did not achieve SVR – 4 were lost to follow-up, 2 relapsed (both SOF-experienced), 2 had end-of- treatment virological failure and 1 discontinued early -Patients tolerated DCV+SOF+RBV regimen very well. 8 patients (10.3%) experienced one or more serious AEs. Common AEs included fatigue, headaches, fatigue, anemia, insomnia and nausea.	-DCF+SOF+RBV is effective and tolerable in patients with HCV genotype 3 infection with compensated cirrhosis Patients with prior failure experience with SOF regimen and HCV GT3 infection are predisposed to failure with DCV+SOF+RBV regimen despite the 24-week duration.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Itokawa et al[319] 2019 **LOE- 2**	Large-scale multicenter, retrospective study ASV/DCV, LDV/SOF or PTV/OBV/r	N = 2162 12 weeks	-Patients ≥ 18 years with HCV genotype 1b infection, compensated cirrhosis, serum HCV-RNA levels > 1.2 log IU/ml at baseline Exclusions – Patients with decompensated cirrhosis, malignant tumors, HIV or Hep B virus coinfection, pregnancy or lactation and contraindicated concomitant drugs for ASC/DCV, LDV/SOF or PTV/OBV/r	-SVR defined as patients who were negative for HCV-RNA for 12 weeks post treatment	-Overall SVR: 93% -Patients that received ASV/DCV, LDV/SOF or PTV/OBV/r achieved an overall SVR rate of 90.0%, 96.9% and 97.6% respectively -SVR in patients with cirrhosis was significantly lower than that in patients without cirrhosis (89.1% vs 95.1%) -Factors that contributed to improved SVR rates for patients included absence of cirrhosis (95% CI 1.40-3.92); absence of previous DAA based treatment (95% CI 7.62-31.11); HCV-RNA level (95% CI 1.66-3.32); wild type NS5A L31/Y93 (95% CI 3.94-11.02); and DAA regimen (LDV/SOF or PTV/OBV/r) (95% CI 6.41-23.04) -Patients that were treatment naïve achieved an SVR rate of 94.1% where in patients that received ASV/DCV, the rate was 91.2%; LDV/SOF group achieved a rate of 98.1% and PTV/OBV/r had a rate of 98.0%	-Presence of cirrhosis, preexisting NS5A RAS, and previous DAA treatment may reduce SVR rates, regardless of DAA regimens

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Miotto et al[320] 2018 **LOE- 2**	Observational real-life cohort SOF + DCV w/w/o RBV for 24 weeks in GT1 patients w/ Child-Pugh B C cirrhosis or prior non-responders to 1st gen PI based treatment Rest of GT1 patients received SOF + DCV or SMV w/w/o RBV for 12 weeks GT2 patients received SOF + RBV for 12 weeks GT3 patients received SOF+DCV w/w/o RBV for 12 weeks	N = 527 24 weeks	-Patients > 18 years with HCV GT 1, 2 or 3 infection These patients were treatment naïve or previously failed PEG-IFN and RBV or to PEG-IFN and RBV + 1st generation PI 51.6% of patients had cirrhosis	-Primary endpoint: SVR12 in ITT and mITT groups -Secondary endpoints: factors that are associated with attaining an SVR rate as well as safety assessment	-Overall SVR rates for ITT were 90.5% and for mITT were 96% -SVR rates were higher in non-cirrhotic (94.2% in ITT and 96.8% in mITT) vs cirrhotic patients (87.1% in ITT and 95.2% in mITT). -SVR rates were higher in patients with Child-Pugh A (88.7% in ITT and 95.7% in mITT) vs Child-Pugh B or C (80% in ITT and 90% in mITT) -SVR rates were higher in patients with genotype 1 (92.1% in ITT and 98.2% in mITT), followed by genotype 2 (84.6% in ITT and 92.7% in mITT) and genotype 3 (84.4% in ITT and 88.4% in mITT). -In the ITT group, lower CCI (p = 0.0014) and absence of cirrhosis (p = 0.0071) were associated with achievement of SVR. -In cirrhotic patients, lower MELD (p = 0.0258), higher albumin (p = 0.0015), and higher eGFR (p = 0.0366) were related with SVR	-SVR rates amongst genotype 1 patients were high and similar to clinical trials and real-life cohorts, while SVR rates among genotype 3 patients were lower than those studies. Since this was an observational study, we cannot conclude that one treatment regimen is superior to another. Moreover, patients in GT1 group with decompensated cirrhosis and prior failure to PI based treatments, received treatment for 24 weeks whereas the rest of GT1 patients received 12 or 24 weeks of treatment and so we cannot

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-In the ITT group, 55 patients did not achieve SVR. Among virologic failures, 63.3% had genotype 3. -8.1% of patients experienced one or more serious AE; Mild anemia (33.9%), Moderate anemia (5.5%), Severe anemia (1.7%)	compare the two groups.
Wei et al[321] 2019 **LOE- 1b**	Phase 3, randomized, international, parallel-group, placebo-controlled, double-blind study elbasvir/grazoprevir Vs placebo	N =489 12 weeks	-Patients ≥ 18 years w/ Hep C genotype 1, genotype 4 or genotype 6 Patients were treatment-naïve, they either had cirrhosis or non-cirrhosis and a baseline HCV RNA ≥ 10,000 IU/mL	-Primary outcome – SVR12 at 12 weeks after end of treatment - Compared safety between 2 treatment arms (immediate/deferred groups(ITG/DTG)) during 12-week blinded period and up to 14 days after un-blinding Monitor AEs	-Overall SVR12 was 94.4% in the combined immediate/deferred-treatment groups -In patients w/ genotype 1b, 1a, and 6, SVR12 rates were 98.2, 91.9%, and 66.7%, respectively -There were no relapses at 24 weeks b/n FW12 and FW24. -Overall incidence of AEs and drug related AEs were similar in ITG and DTG vs placebo treatment groups (51.0% and 21.4% vs 50.4% and 21.1% respectively) -Common AEs reported include – upper respiratory infections, fatigue and headache.	-The use of elbasvir/ grazoprevir for the treatment of HCV genotype 1 infections for 12 weeks is effective in treatment naïve patients. Also, this study had high SVR12 and SVR24 rates in patients with no difference in safety (AEs) in ITG and DTG placebo treatment groups

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Hernández-Conde et al[322] 2018 **LOE- 2**	Retrospective randomized controlled trial (real world study) elbasvir/grazoprevir w/w/o ribavirin	N = 588 28 weeks	-Patients from Spain with HCV infection	-Virologic response (SVR12) defined as undetectable HCV RNA and determined at the end of treatment (EOT) and at week 12 post treatment -Adverse events – collected from initiation of drug treatment to week 12 after EOT	-Overall SVR12: 96.9% -SVR12 rates achieved were 91.2% in ITT group and 96.9% in modified ITT group. -SVR rates in treatment-experienced vs treatment-naïve patients were not significantly different (97.7% vs 98.7%; P = 0.5) -Overall SVR12 rates did not change significantly between GT groups (GT1a – 97.7%; GT1b – 98.6%; GT4 – 98.1%). SVR12 rates were also not significantly different based on fibrosis stage. -In patients with cirrhosis SVR12 was 95.9% -There were 80 reported AEs and this led to 3 patients discontinuing the study. The most common AEs included GI symptoms and anemia	-Overall EBR/GZR achieved high SVR12 rates in overall patients, treatment naïve patients, and treatment experienced patients w/ or w/o cirrhosis The rate of AEs in this study was 10% lower than other studies

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Pariente et al[323] 2019 **LOE- 2**	Multicenter, prospective, observational cohort study sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, sofosbuvir/simeprevir, sofosbuvir/ribavirin	N = 1123 patients 24 weeks	-Patients ≥ 18 (treatment naïve or experienced) years with chronic hep C with detectable HCV-RNA treated with interferon-free regimen	-SVR rate -Tolerance	-SVR rate for 12-24 weeks after the end of treatment was 91% (95% CI: 89.2-92.5%) with no difference according to age -5.6% of patients experienced AEs with 8.1% occurring in those greater than 64 years old. -Self-accessed global tolerance was excellent and identical across all age groups.	-Age did not affect the overall SVR rate in this study This study suggests that age per se should not be considered a contraindication to antiviral treatment, however frailty, comorbidities and associated treatments should be carefully evaluated.
Boerekamps et al[324] 2019 **LOE- 2**	Open-label, multicenter, single arm, phase 3b trial grazoprevir/elbasvir for 8 weeks	N = 146 8 weeks	-Patients ≥ 18 years irrespective of HIV status with acute HCV genotype 1 or 4 infection for 26 weeks or less	-The primary outcome was SVR12 in all patients who started treatment The secondary outcomes were safety, SVR12 in genotype 1 and 4 separately and in all patients excluding patients lost to f/u or d/c treatment for other reasons other than virologic failure	-There were 146 patients assessed with a recently acquired HCV infection, of whom 86 were enrolled and 80 initiated therapy, all within 6 months after infection. -Overall, 99% of patients achieved SVR12 (N=78/80; 995% CI 93-100), including 14 patients with NS5A -Counting reinfections as treatment failures, 94% of patients achieved SVR12 (N=75/80; 95% CI86-98) -The percent of patients achieving	-The authors concluded that 8 weeks of grazoprevir/ elbasvir is highly effective and tolerable in patients with acute HCV genotype 1 or 4 infection. Even though the study had a short duration, a high SVR12 was

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
				Adverse effects	SVR12 for genotype 1 and 4 were similar (100% vs. 97%; P= 0.4). -Reported drug-related adverse effects include fatigue (14%), headache (9%), mood changes (6%), dyspepsia (6%), insomnia (9%), concentration impairment (5%) and dizziness (5%). No adverse effects led to study discontinuation.	achieved with 8 weeks of treatment.
Ogawa et al[325] 2018 **LOE- 1b**	Multicenter, real world cohort study elbasvir + grazoprevir	N = 282 12 weeks	-Japanese patients aged 20 years and older with HCV GT1 infection Exclusion – Decompensated cirrhosis w/ Child-Pugh B or C, viable hepatocellular carcinoma at baseline and + antibody to HIV or + Hep B surface antigen	-SVR12 rates in the intention to treat (ITT) and per protocol (PP) populations Safety - AEs	-Overall SVR12 rates achieved in ITT and PP groups were 97.5% and 98.6% respectively. -SVR12 rates were 98.8% for patients with CKD stage 3–5 and 95.0% for those with stage 5D on hemodialysis. -High SVR rates were observed in all subgroups, including CKD stage 3–5, 5D (hemodialysis), older age (≥75 years), cirrhosis, and history of HCC. -SVR12 rate of patients with NS5A RAS (90.5%) was significantly lower than that of those non-NS5A RAS (100%; p=0.03).	-This study showed that the use of EBR + GZR for 12 weeks was highly effective and with a low rate of AEs, regardless of CKD status

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-AEs deemed serious (hematological and lab abnormalities) were rare. Serious elevation of AST was experienced by 1.8% of patients and of ALT by 1.4% of patients during treatment. -6 patients discontinued treatment due to AEs, but all achieved SVR	
Abdelaty et al[328] 2020 **LOE-2**	Randomized, open-label trial sofosbuvir 400 mg/daclatasvir 60 mg Vs sofosbuvir 400 mg/ ledipasvir 90 mg	N=100 12 weeks	-Adults with Chronic hepatitis C genotype 4 who were treatment naïve and non-cirrhotic. Exclusions criteria included pregnancy, advanced liver disease, cardiac problems, drug/alcohol induced liver injury and HIV co-infection.	-The sustained virologic response 12 weeks post-treatment (SVR12) (HCV RNA < Lower Limit of Quantification (LLOQ)). -Safety	-Regarding the primary endpoint, SVR12 values and relapse rates did not show any significant difference between the treatment groups. The SVR12 values of sofosbuvir plus daclatasvir and sofosbuvir plus ledipasvir post 12 weeks treatment, were 96% and 98% respectively. -The mean ± SD ALT and AST levels decreased significantly from 35.3±10.58 to 20.2±5.64 ($p<0.001$), and from 34.3±10.96 to 22.4±5.82 ($p<0.001$) post 12 weeks treatment of sofosbuvir plus daclatasvir, respectively. Furthermore, there was a significant decrease in the mean±SD ALT and AST levels from 38.2±15.79 to 19.6±5.58	-This study concluded that treatment results in both groups, sofosbuvir/ daclatasvir and sofosbuvir/ ledipasvir, were non-statistically different and achieved high SVR12 rates in adults with genotype 4 who were treatment naïve and non-cirrhotic. In addition, both treatment regimens were well tolerated and did

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					(p<0.001), and from 37.6±16.64 to 20.6±5.86 (p<0.001) post 12 weeks treatment of sofosbuvir plus ledipasvir, respectively. -The most common side effects were fatigue and headache as experienced by 8%, 10% and 20%, 4% for sofosbuvir/daclatasvir and sofosbuvir/ledipasvir, respectively. No serious adverse effects were reported.	not develop any severe side effects that may lead to therapy discontinuation.
Soria et al[327] 2019 LOE-2	Observational cohort study sofosbuvir (SOF) + daclatasvir (DAC) Vs SOF/velpatasvir (VEL) Vs glecaprevir/ pibrentasvir (GLE/PIB)	N=1544 Follow-up: The treatment duration was 12 or 24 weeks for patients treated with SOF + DAC, 12 weeks for patients treated with SOF/VEL and 8, 12 or 16 weeks for GLE/ PIB.	-Adults with chronic hepatitis C, genotype 3 (HCV-GT3) with and without cirrhosis.	-Sustained virologic response 12 weeks after treatment completion (SVR12).	-Overall, SVR12 was 95.7%, and was similar between the three treatment groups: 94.8% in SOF + DAC, 97.6% in SOF/VEL, 96.7% in GLE/PIB (p=0.065). At univariate analysis, SVR12 was associated with female gender (97.9% vs 94.8%, p=0.007) and lower median Log10HCV-RNA at baseline (5.87 vs 6.20, p=0 .001), while the slightly lower response rate in cirrhotic patients (94.9% vs 96.7%) and in those not using ribavirin (RBV) (94.6% vs 96.5%) were not statistically significant (p=0.097 and 0.089 respectively). -In non-cirrhotic patients SVR12 was 95.3% in SOF + DAC, 98.6% in	-The results of this observational cohort of HCV-GT3-infected patients with a high proportion of cirrhosis suggest a high success rate with no significant difference between SOF + DAC, SOF/ VEL and GLE/PIB. The slight advantage of SOF/VEL on SOF + DAC was significant only in the absence of RBV.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					SOF/VEL, 96.1% in GLE/PIB (relative risk [RR] of SVR12 for SOF/VEL vs SOF + DAC 1.03 [95% confidence intervals, CI, 1.01-1.06]); in cirrhotic patients SVR12 was 94.9% in SOF + DAC, 93.6% in SOF/VEL, 100% in GLE/PIB (RR of SVR12 for GLE/PIB vs SOF + DAC 1.05 [95% CI 1.03-1.07]). -A significant difference of SVR12 was observed in SOF/VEL recipients between cirrhotic and non-cirrhotic patients (73/78, 93.6% vs 277/281, 98.6%, p=0.026 respectively).	
Belperio et al[346] 2019 LOE-2	Observational, cohort study sofosbuvir/velpatasvir/ voxilaprevir (SOF/VEL/VOX)	N=573 12 weeks after end of treatment (EOT)	-Adults with chronic hepatitis C, genotypes 1-4, who are direct-acting antiviral (DAA) experienced.	-Sustained virologic response defined as HCV RNA below the lower limit of quantification (LLOQ) at least 12 weeks or more after the end-of-treatment (EOT).	-There were 573 patients who initiated SOF/VEL/VOX at 104 VA facilities of whom 490 were genotype 1, 20 genotype 2, 51 genotype 3 and 12 genotype 4. Overall SVR rates were 90.7% (429/473) for genotype 1, 90.0% (18/20) for genotype 2, 91.3% (42/46) for genotype 3 and 100.0% (12/12) for genotype 4. -Among those who completed 12 weeks of SOF/VEL/VOX, SVR rates were reduced in genotype 1 patients with a history of hepato-	-SOF/VEL/VOX achieved high SVR rates overall across all four genotypes irrespective of advanced liver disease and generally irrespective of prior DAA experience. SVR rates were lower among genotype 1, 2 and 3 patients with prior SOF/VEL

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					cellular carcinoma (HCC) compared to those with no HCC history (81.2% (13/16) vs 95.7% (396/414; p=00.04). -For genotype 1 patients, SVR rates were uniformly high regardless of the prior HCV antiviral class a patient received: 92.4% (61/66) with prior NS3/4A + NS5A-only experience, 87.9% (94/107) with prior NS3/4A + NS5A+NS5B experience and 91.3% (274/300) with prior NS5A + NS5B-only experience. -Most genotype 3 patients had prior NS5A + NS5B-only experience, of whom 90.2% (37/41) achieved SVR. By prior regimen, SVR rates were 88.9% (16/18) with prior ledipasvir/SOF experience, 90.9% (10/11) with prior daclatasvir + SOF and 100.0% (7/7) with prior SOF + ribavirin. SVR rates were somewhat lower in genotype 3 patients who received prior SOF/VEL (84.6%, 11/13).	experience suggesting an alternative regimen should be considered in these patients. These results need to be confirmed in randomized trials.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Buggisch et al[337] 2019 **LOE-2**	Retrospective, observational, single-center cohort study sofosbuvir/velpatasvir (SOF/VEL) 12-week regimen (n=115) Vs ledipasvir/sofosbuvir (LDV/SOF) 8-, 12- or 24-weeks regimens (n=249)	N=364 12 weeks after end of treatment (EOT)	-Adults with chronic hepatitis C who were treated with either SOF/ VEL or LDV/SOF, ± ribavirin (RBV).	-Sustained virologic response 12 weeks after cessation of treatment (SVR12). -The incidence and type of grade 3 or 4 AEs, treatment discontinuation and/or hospitalization were collected by the study center through a standardized questionnaire.	-The majority of patients treated with SOF/VEL or LDV/SOF 8 weeks were treatment naïve (TN) (range: 74.3% among SOF/VEL 12 weeks + RBV, to 97.7% among LDV/SOF 8 weeks), while most patients treated with LDV/SOF ± RBV 12 or 24 weeks were TE (63.3%). Among the treatment exposed (TE) patients across all regimens in this study, most did not receive a previous DAA (range: 77.8% among SOF/VEL 12 weeks + RBV, to 100% among LDV/SOF 8 weeks). -A total of 112 patients treated with SOF/VEL regimens completed the full treatment course and were included in the final per-protocol analyses. SVR12 was achieved in 99.1% (111/112) of patients overall on SOF/VEL ± RBV 12 weeks, across all GT and patient subpopulations. The patient who did not achieve SVR12 was a 69-year-old who was GT1, cirrhotic, TN, treated without RBV. -Among the 249 LDV/SOF patients	-This study confirms the effectiveness of SOF/VEL and LDV/SOF therapies in the real world, with SVR12 results comparable to those achieved in clinical trials. The results suggest that SOF/VEL as a 12-week pan-genotypic treatment option is convenient and effective.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					participating in the study, 129 (49.8%) received LDV/ SOF 8 weeks and 120 (50.2%) received LDV/SOF ± RBV for 12 or 24 weeks. Overall SVR12 rate was 99.2% (128/129) for patients on LDV/SOF 8 weeks, and 93% (111/120) for patients on LDV/SOF ± RBV 12 or 24 weeks. Among the 9 patients who did not achieve SVR12 under LDV/SOF ± RBV 12- or 24-weeks regimens, 6 were treated with LDV/SOF ± RBV 12 weeks, and the remaining 3 with LDV/SOF + RBV 24 weeks. -Only 1 (0.6%) SOF/VEL patient experienced any grade 3/4 AE, 13 (5.2%) LDV/SOF patients reported at least one grade 3/4 AE. None of the AEs led to hospitalization or death.	
Charatchar-oenwitthaya et al[341] 2020 LOE-2	Retrospective, observational, multicenter cohort study in Thailand	N=1021	-Adults with hepatitis C virus (HCV) infection genotypes 1,2,3,4 and 6 treated with sofosbuvir-based regimens.	-SVR, defined as undetectable HCV RNA 12 weeks after the end of treatment (SVR12).	-Patients were infected primarily with HCV genotypes 1 (49.5%), 3 (31%), or 6 (16%). -Five hundred and twenty-two patients (51.1%) had a diagnosis of cirrhosis. The majority of cirrhotic patients were treated with 12 weeks of DAC + SOF with (43.3%)	-This multicenter Thai cohort provided clinically relevant information on the effectiveness and safety of SOF plus the NS5A inhibitors, e.g., DAC, LDV, or

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	12 to 24 weeks of daclatasvir (DAC) plus sofosbuvir (SOF) (n = 767) Vs ledipasvir (LDV) / sofosbuvir (n = 197) Vs sofosbuvir/ velpatasvir (VEL) (n = 57), all with or without ribavirin (RBV).	Follow-up: 12 weeks after end of treatment (EOT)			or without RBV (10.7%), followed by 12 weeks of LDV/SOF with (14.2%) or without RBV (2.5%), and 12 weeks of SOF/VEL with (3.1%) or without RBV (4.2%). -Overall, SVR12 was achieved by 97.9% (95% CI, 96.8%–98.7%) of the 968 patients in the mITT analysis, including 98.0% (95% CI, 96.7%–98.8%) of patients treated with DCV + SOF, 97.9% (95% CI, 94.8%–99.2%) of patients treated with LDV/SOF, and 96.5% (95% CI, 88.1%–99.0%) of those treated with SOF/VEL. -The SVR12 rates were generally comparable across treatment regimens. The SVR12 rates were achieved by 99.2% of patients (479 of 483) infected with HCV genotype 1, all 14 patients (100%) with genotype 2, 96.7 of patients (293 of 303) with genotype 3, 90.9% of patients (10 of 11) with genotype 4, 96.7% of patients (147 of 152) infected with genotype 6, and all five patients (100%) with unspecified genotype.	VEL in a large cohort of patients infected with diverse HCV genotypes and high proportions of treatment-experienced patients and those with cirrhosis.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Degasperi et al[333] 2019 LOE-2	Retrospective, observational, multicenter cohort study sofosbuvir/velpatasvir/ voxilaprevir (SOF/ VEL/VOX) 400/100/100 mg/day for 12 weeks with or without ribavirin (RBV)	N=179 Follow-up: 12 weeks after end of treatment (EOT)	-Adults with HCV starting antiviral treatment with SOF/VEL/VOX	-On-treatment virologic response was defined as HCV-RNA below the limit of quantification (LLOQ) or undetectable by either the Abbott-RT PCR (lower limit of detection 12 IU/ml) or COBAS TaqMan assay (lower limit of detection 15 IU/ ml) at treatment week 4 (4-week virologic response) and at EOT (EOT response). SVR was defined as undetectable HCV-RNA 4 (SVR4) and 12 (SVR12) weeks after treatment completion.	- HCV genotype was 1 in 58% of the patients (1b 33%, 1a 24%, 1 nc 1%), 2 in 10%, 3 in 23% and 4 in 9%, respectively. Most patients had failed SOF/VEL (20%), SOF/ledipasvir (LDV) (20%) or ombitasvir/paritaprevir-r (OBV/PTV-r) + dasabuvir (DSV) (17%). Overall, 94% of patients had failed an NS5A- and 39% an NS3-containing regimen. -At baseline, 78 out of 79 (99%) cirrhotic patients were Child-Turcotte-Pugh (CTP) score A; 16 (9%) patients had a previous history of HCC, and 2 compensated cirrhotics were on the liver transplant (LT) waiting-list for HCC. -Overall, on-treatment virologic response at week 4 was achieved by 108 out of 145 (74%) patients with available on-treatment data: HCV-RNA was <LLOQ in 45 (31%) and undetectable in 63 (44%), respectively. -By intention to treat (ITT) analysis, 169/179 (94%) patients	-In a retrospective cohort of patients with hepatitis C virus infection and a prior direct-acting antiviral failure, this study demonstrated effectiveness (98% and 96% sustained virologic response rates at week 4 and 12, respectively) of SOF/VEL/VOX. Cirrhosis and hepatocellular carcinoma onset were the only features associated with treatment failure.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					achieved the SVR4 and 162/179 (91%) the SVR12: by analyzing SVR rates according to HCV genotype, treatment effectiveness was suboptimal in HCV-3 patients, as 98/103 (95%) HCV-1, 17/18 (94%) HCV-2, 33/42 (79%) HCV-3 and 14/16 (88%) HCV- 4 patients achieved the SVR12, respectively (p = 0.02). -At PP univariate analysis, cirrhosis and HCC onset were the only features associated with a lack of SVR. SVR12 rates were 100% vs. 91% in F0-F3 vs. F4 patients (p = 0.005) and 71% vs. 97% in patients with or without HCC onset after treatment start (p = 0.02).	
Deutsch et al[343] 2020 LOE-2	Open-label, observational, multicenter study. ombitasvir/paritaprevir/ritonavir and dasabuvir (3D) ± ribavirin (RBV) for 12/24 weeks	N=39 Follow-up: 12 weeks after end of treatment (EOT)	-Adults with HCV genotype 1 who were previously null/partial responders or relapsers to telaprevir, boceprevir or simeprevir+pegIFN/RBV. Only patients with	-The percentage of patients achieving SVR12 (single last HCV RNA < 12 IU/mL 12 weeks after the last dose of medications). -Secondary outcomes were patient reported outcomes, adverse events and	-The majority of the 39 patients were previously treated with telaprevir (53.8%), 43.6% with boceprevir and only one patient with simeprevir. -There was no virologic relapse among patients that completed the study, thus the per-protocol SVR12 rate was 97.3% and comparable to 97% SVR12 described in historical cohorts	-In this open-label, prospective, multi-centre clinical trial, treatment of HCV infected patients that failed previous PI treatment with a combination of ombitasvir/ paritaprevir/ ritonavir and dasabuvir for 12/24

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			virologic failures and not dis-continuation due to adverse events were included.	resistance associated variants.	(p=1.000, Chi-square test). There were two early treatment terminations both did not achieve SVR12. Thus, according to the intention-to-treat protocol, the SVR12 rate was 36/39 (92.3%) and comparable to the historical cohort SVR12 (92.3% vs. 97%, p=0.349, Chi-square test). -Out of 39 patients, two patients had an early drop-out – one after a few days because of palpitations, leg edema and general weakness and another after 6 weeks because of an acute psychotic episode and admission to a psychiatric ward.	weeks ± RBV, resulted in SVR12 rates of 92% of all patients, and 97% of those who completed the treatment, similar to those reported with other second-generation treatment regimens.
Llaneras et al[335] 2019 LOE-2	Prospective, multicenter observational study sofosbuvir, velpatasvir, and voxilaprevir (SOF/VEL/VOX) 400mg /100mg/100mg QD x 12 weeks	N=137 Follow-up: 12 weeks after end of treatment (EOT)	-Adults with chronic hepatitis C, including those with compensated cirrhosis, who had previously failed combined therapy with 2 DAAs in an interferon-free regimen. Patients	-The percentage of patients with a sustained virologic response stratified by genotype (GT), defined as persistently undetectable HCV RNA at week 12 after completion of treatment (SVR12). The secondary	-All patients had previously received a DAA-based interferon free regimen with the following combinations: sofosbuvir based regimen plus an NS5A inhibitor or NS3/4A inhibitor in 88 patients (64%), NS3/4A inhibitor-based regimen plus an NS5A inhibitor in 15 (11%), non-nucleoside NS5B plus NS5A plus NS3/4A inhibitor in 28 (20%), and other DAA combinations within clinical trials in 6 (4%).	-The results of this real-world study suggest that the SOF/VEL/VOX combination is safe and effective for patients with previously treated HCV, supporting the results reported in clinical trials. The overall SVR12 rate was

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			coinfected with HIV and those with hepato-cellular carcinoma (HCC) were also enrolled.	endpoint was treatment-associated adverse events.	-SVR12 was achieved in 95% (128/135). SVR12 rates by HCV genotype were 100% (29/29) in patients with GT1a, 100% (53/53) in GT1b, 80% (24/30) in GT3, 100% (7/7) in GT2 and 93% (13/14) in GT4. The SVR12 rate was 89% (41/46) in cirrhotic patients and 98% (87/89) in non-cirrhotic patients (p = 0.05). Overall, SVR12 rates were higher in the non-3 genotypes (99%) than in GT3 (80%) (OR 26; 95% CI 3–226). GT3 patients with cirrhosis showed the lowest SVR12 rates: only 69% compared to 97% in non-GT3 cirrhotic patients (OR 24; 95% CI 2.7–213). -Only 25 (19%) mild adverse episodes were reported during treatment. Headache was the most common (36%), followed by asthenia (32%), diarrhea (12%), and nausea (12%).	95%, although GT3-infected patients, particularly those with underlying liver cirrhosis, had considerably lower SVR rates.
Lok et al[334] 2019 LOE-2	Randomized, open-label study	N=177	-Adults with hepatitis C (HCV) genotype 1 infection who experienced	-SVR12 with preplanned comparisons between arms A: G/P12 and B: G/P16-	-SVR12 was achieved in 162 of 177 (91.5%) patients overall, 70 of 78 (90%; 95% CI, 81%–95%) in A: G/P12, 46 of 49 (94%; 95% CI, 83%–98%) in B: G/P16-NC, 18 of	-This open-label, randomized study for GT1 patients who failed prior treatment with

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
	glecaprevir/ pibrentasvir 300mg / 120mg for 12 weeks (G/P12) Vs glecaprevir/ pibrentasvir 300mg / 120mg for 16 weeks in non-cirrhotic patients (G/P16-NC) Vs glecaprevir/ pibrentasvir 300mg / 120mg with ribavirin for 12 weeks (G/P-RBV12) Vs glecaprevir/ pibrentasvir 300mg / 120mg for 16 weeks in cirrhotic patients (G/P16-Cirr)		treatment failure after sofosbuvir plus an NS5A inhibitor ± RBV taken for at least 4 weeks with no documented noncompliance.	NC (noncirrhotics), and arms C: G/P-RBV12 and D: G/P16-Cirr (compensated cirrhotics). The secondary efficacy end points were the difference in SVR12 rates between G/P given for 12 weeks (A: G/P12 and C: G/P-RBV12 combined) and G/P given for 16 weeks (B: G/P16-NC and D: G/P16-Cirr combined) and the difference in on-treatment virologic failure and relapse between arms A: G/P12 and B: G/P16-NC, and arms C: G/PRBV12 and D: G/P16-Cirr.	21 (86%; 95% CI, 65%–95%) in C: G/P-RBV12, and 28 of 29 (97%; 95% CI, 83%–99%) in D: G/P16-Cirr. -SVR12 was achieved in 88 of 99 (89%) patients who received 12 weeks G/P and in 74 of 78 (95%) who received G/P for 16 weeks. All 34 GT1b patients who could be assessed achieved SVR12; 1 died before SVR12 assessment. Both patients with other GT1 subtypes (non-1a, non-1b) achieved SVR12. SVR12 was achieved in a numerically lower proportion of GT1a patients, 65 of 75 (87%; 95% CI, 77%–93%) who received G/P for 12 weeks and 61 of 65 (94%; 95% CI, 85%–98%) who received G/P for 16 weeks. -Virologic failure occurred in 13 of 140 (9.3%) patients with GT1a infection, 0 of 35 with GT1b, and 0 of 2 with GT non-1a, non-1b; in 4 of 50 (8%) cirrhosis and 9 of 127 (7.1%) noncirrhosis patients; and in 9 of 99 (9.1%) patients who received 12 weeks of G/P and 4 of 78 (5.1%) who received 16	NS5A inhibitor plus sofosbuvir, demonstrated high SVR12 rates with G/P when given for 16 weeks. SVR12 rates for 16-week G/P treatment were 94% among non-cirrhosis patients and 97% among cirrhosis patients. These results support FDA approval of 16-week G/P as a retreatment option for GT1 sofosbuvir plus NS5A inhibitor treatment failures.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					weeks of G/P. Virologic failure (all relapses) occurred in 1 of 9 (11.1%) patients who had HIV co-infection, 3 of 15 (20%) who had liver transplantation, and 3 of17 (17.7%)who had a history of HCC.	
Margusino - Framiñán et al[347] 2020 **LOE-2**	Prospective, observational cohort study sofosbuvir/velpatasvir 400mg / 100mg QD ± ribavirin (SOF/VEL ± RBV) for 12 to 24 weeks Vs glecaprevir/ pibrentasvir 100mg / 40mg 3 tabs daily (GLE/PIB) for 8 to 16 weeks	N=76 Follow-up: 12 weeks after end of treatment (EOT)	-Adults with genotype 3 hepatitis C virus (G3-HCV) infection. The patients included in the analysis were permitted to be naïve or treatment-experienced to peg-INF+ RBV or DAAs, in all stages of hepatic fibrosis, including patients with decompensated cirrhosis or portal hypertension. Patients with HIV co-infection	-The proportion of patients with SVR12, defined as an undetectable HCV ribonucleic acid (HCV-RNA) 12 weeks' post-treatment. -Safety	-All patients achieved virologic suppression at the end of treatment, but three of them relapsed within 12 weeks of follow-up, so the overall SVR12 was 96%. -The SVR12 was 96% in patients treated with SOF/VEL±RBV compared with 97% in patients treated with GLE/PIB (P=0.7). The SVR12 was 83% in cirrhosis patients, compared with 98% in patients without cirrhosis (P=0.09). -The SVR12 was 100% in patients with low fibrosis, compared with 86% in those with high fibrosis (P=0.03). The SVR12 was 96% in all treatment-naïve patients compared with 100% in treatment-experienced patients (P=0.57).	-The results of this observational study suggest SOF/ VEL±RBV or GLE/PIB show a high antiviral effectiveness in individuals infected with G3-HCV, with an overall SVR12 rate of 96% and no significant differences in the effectiveness or the safety of the two treatment regimens. Further research is needed to validate these results.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			and those who had had a previous liver transplant were included.		-Moderate AEs secondary to SOF/VEL±RBV included fatigue/ asthenia, ocular pain, anxiety, dry skin, irritability and insomnia. Moderate AEs secondary to GLE/PIB included only fatigue/ asthenia. No patients experienced an SAE or required withdrawal, attention in the Emergency Department or hospitalization as a result of an AE, and none of the patients died during the study period.	
Ogawa et al[339] 2019 **LOE-2**	Retrospective, multicenter cohort study glecaprevir (GLE) 300mg and pibrentasvir (PIB) 120mg QD for 8 weeks (DAA treatment-naïve or non-cirrhotic) to 12 weeks (cirrhotic or DAA treatment-experienced)	N=314 Follow-up: 12 weeks after end of treatment (EOT)	-Adults with confirmed chronic HCV genotype 1 or 2 infection. Exclusion criteria included: (i) mixed HCV genotype; (ii) de-compensated cirrhosis with a Child–Pugh B or C score; (iii) viable HCC within 3 months	-Sustained virologic response categorized as undetectable HCV-RNA (target not detected) at week 12 after the end of treatment (SVR12). Safety and tolerability data at each participating site were collected from patient medical records recorded throughout the treatment duration and 1-month post-	-Among patients infected with HCV genotype 1, 73.8% (n = 90) were treatment-naïve, 27.9% (n = 34) had cirrhosis, 17.2% (n = 21) had diabetes mellitus, 12.3% (n=15) had a history of HCC prior to GLE/PIB treatment, and 4.9% (n = 6) were receiving hemodialysis. Of the treatment-experienced patients (n=32), 20 had previously received all-oral DAAs, 15 asunaprevir (ASV) plus daclatasvir (DCV), and 5 ledipasvir (LDV)/ sofosbuvir (SOF). -Of those with HCV genotype 2, 79.2% (n=152) were treatment-	-The findings from this study suggest that treatment with GLE/PIB for HCV genotypes 1 and 2 resulted in a high rate of SVR12 and a low rate of serious adverse events in a real-world clinical setting, including for patients with compensated cirrhosis, severe renal impairment, or previous all-oral DAA treatment for

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			before treatment initiation and (iv) positivity for antibody to HIV or positivity for hepatitis B surface antigen.	treatment.	naïve, 26.0% (n = 50) had diabetes mellitus, 22.9% (n=44) had cirrhosis, 7.8% (n = 15) had a history of HCC treatment prior to GLE/PIB, and 7.4% (n = 17) were receiving hemodialysis. Of the treatment experienced patients, 21 had previously received SOF and ribavirin (RBV). -Among HCV genotype 1-infected patients, the overall SVR12 rates in the ITT and per-protocol (PP) populations were 97.5% (119/122) and 99.2% (119/120), respectively. Notably, the SVR12 rate of patients with previous all-oral DAA failure, including ASV +DCV (15/15) and LDV/SOF (5/5), was 100%. -Among HCV genotype 2-infected patients, the overall SVR12 rates in the ITT and PP populations were 95.3% (183/192) and 98.9% (183/185), respectively. The SVR12 rate of patients with previous SOF + RBV failure was 100% (20/20). -The most common adverse	HCV. These results need to be validated with further research.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					events were pruritus (7.3%) and fatigue (5.4%). Serious adverse events due to hematological and laboratory abnormalities were experienced by less than 1% of the patients.	
Ogawa et al[342] 2020 **LOE-2**	Retrospective, multicenter cohort study ledipasvir/sofosbuvir (LDV/SOF) 90mg / 400mg for 12 weeks; Vs glecaprevir/ pibrentasvir (GLE/PIB) 300 mg / 120 mg for 8 to 12 weeks depending on DAA treatment experience and evidence of cirrhosis;	N=265 Follow-up: 12 weeks after end of treatment (EOT)	-Adults with confirmed chronic HCV genotype (GT)2 infection. Exclusion criteria included: (i) mixed HCV genotype; (ii) de-compensated cirrhosis with a Child–Pugh class B or C; (iii) viable hepato-cellular carcinoma within 3months before treatment initiation and (iv) positivity for antibody to human immune-	-SVR was categorized as undetectable HCV RNA (target not detected) at week 12 after the end of treatment (SVR12). -SVR12 was also assessed in the modified intention-to-treat (mITT) population, which excluded patients with non-virologic failure, including those who dropped out before the SVR12 assessment.	-The virologic response to LDV/SOF revealed overall SVR12 rates in the ITT and mITT populations of 94.8% (55/58) and 96.5% (55/57), respectively. Notably, both patients with previous SOF +RBV failure achieved SVR12. -A propensity matched score (PSM) analysis revealed the overall SVR12 rates in mITT populations treated with LDV/SOF and GLE/PIB were 96.1% (49/51) and 98.0% (49/50), respectively (p=0.57). No significant difference in the frequency of any adverse event was found between the LDV/SOF (17.3%) and GLE/PIB groups (25.0%; p=0.34). No serious adverse events or death were found in either treatment group.	-In this retrospective study of adults with HCV GT2, the mITT analysis of LDV/SOF had a high rate of SVR (96.5%, 55/57), including for patients who were treatment experienced or with compensated cirrhosis. In the PSM analysis, we found that HCV GT2 patients treated with LDV/SOF had favorable adverse event profiles and similar SVR rates to patients treated with GLE/PIB for 8–12 weeks.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
			deficiency virus or positivity for hepatitis B surface antigen.			
Pariente et al[345] 2019 **LOE-2**	Prospective, multicenter observational study sofosbuvir/ledipasvir (38%), sofosbuvir/ daclatasvir (32%), sofosbuvir/simeprevir (17%), ombitasvir + paritaprevir + ritonavir (5%) (with dasabuvir 3.5%), and sofosbuvir/ ribavirin (8%). Ribavirin was given to 24% of patients.	N=1123 Follow-up: 12-24 weeks after end of treatment (EOT)	Adults treated for chronic hepatitis C (CHC) at 24 French hospitals with direct acting antivirals (DAA)	-Sustained virologic response 12–24 weeks after treatment (SVR 12-24). Secondary outcomes included severe adverse events (SAE).	-Fifty-five percent of patients were treatment-experienced, 128 (20.7%) with telaprevir or boceprevir. Cirrhosis was present in 553 (49.2%) patients and was decompensated in 40 (7.2%). There were 455 patients (86.8%) with Child-Pugh Class A cirrhosis and 228 (44.2%) with esophageal varices. Hepatocellular carcinoma was previously diagnosed in 24 patients (2.2%). HIV infection was present in 99 (8.8%) patients, and 8 (0.7%) patients were HBsAg positive. -The overall SVR rate was 91.0% (95% CI: 89.2–92.5). The SVR rate was 405/456 (89.0%), 51/60 (85.0%), and 6/9 (66.7%) in Child-Pugh A, B and C patients, respectively. Treatment failure was observed in 100 patients: 58 relapses, 5 breakthrough/non-responses, 13 SAEs, 1 premature treatment discontinuation by the patient, and 23 lost to follow-up.	-This observational study suggests that the high SVR12 rates seen in clinical trials of DAAs can be replicated in large cohorts of patients treated in real-life conditions. Second generation DAAs combinations are as effective and well tolerated in a "real- world" population as in clinical trials. Further research is needed in special populations such as patients with renal insufficiency.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-Logistic regression analysis identified 4 independent predictors of SVR: body weight, previous hepatocellular carcinoma, albumin and treatment combination (SOF/SIM, SOF/DCV and SOF/LDV were better than SOF/RBV alone). -Logistic regression analysis of 553 patients with cirrhosis identified previous hepato-cellular carcinoma as an independent predictor of SVR (OR: 0.22 [95% CI: 0.09–0.58], p=0.002) and treatment combination (SOF/DCV: OR 3.39 [95% CI: 1.38–8.31], (p=0.008) and SOF/LDV: OR 2.39 [95% CI: 0.98–5.88], (p=0.06)). -The frequency of SAE was similar in patients treated with SOF/SIM (6.6%), SOF/DCV (4.6%) and SOF/LDV (4.8%), and in patients receiving or not sofosbuvir (5.2% vs. 3.4%, respectively, p=0.76) but was greater in patients treated with ribavirin (8.5% vs. 4.6%, p=0.02).	

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
Ueda et al[340] 2019 LOE-2	Multicenter, observational cohort study glecaprevir (300 mg/day) and pibrentasvir (120 mg/day) for 8 to 12 weeks	N=25 Follow-up: 12 weeks after end of treatment (EOT)	-Liver transplant recipients with chronic hepatitis C. Eligibility criteria included (1) 18 years of age or older, (2) chronic HCV infection, and (3) status post liver trans-plantation. Patients with decompensated liver disease were excluded from the study. DAA-naïve patients with genotype 1 or 2 HCV infection without cirrhosis received 8 weeks of treatment, and the other patients were treated for 12 weeks.	-Sustained virologic response 12 weeks after completion of treatment (SVR12). Efficacy was assessed among patients in the intent-to-treat (ITT) population defined as those who received at least one dose of study drug, and in the modified ITT (mITT) population, which excluded patients who did not achieve SVR12 for reasons other than virologic failure. Secondary outcomes included adverse event monitoring.	-Of the 25 patients treated with glecaprevir and pibrentasvir, 24 completed the treatment protocol. All 24 patients who completed the 8- or 12-week treatment protocol achieved SVR12. SVR12 rates were 98% (24 out of 25 patients) in the ITT population and 100% (24 of 24 patients) in the mITT population after excluding the patient who discontinued treatment due to an adverse event (nausea). -The SVR12 rate in patients with HCV genotype 1 and 2 was 100% (21 of 21 patients) and 75% (3 of 4 patients), respectively. All the patients with prior DAA failure (n = 6), jaundice (serum bilirubin level [3 mg/dL, n = 4), and liver cirrhosis (n = 4) achieved SVR12. Seven of 8 patients (88%) with severe renal impairment (eGFR\30 mL/min/1.73 m2) and all of 4 patients with hemodialysis achieved SVR12. -Adverse events occurred in 6 of 25 patients (24%), including serious adverse events in 2	-The results of this small, observational study suggest that an 8- and 12-week regimen of glecaprevir and pibrentasvir in patients with recurrent HCV genotype 1 or 2 infection after liver transplantation is effective and safe. The results of this study are limited by the non-randomized design and small sample size. Further research is needed to validate these results.

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					patients (8%). Treatment was discontinued after treatment day 3 in one patient due to nausea. One patient had idiopathic melena, once at 4 weeks from the initiation of treatment and once after 5 weeks, which recovered spontaneously.	
Zarębska-Michaluk et al[344] 2020 LOE-2	Retrospective, multicenter study ombitasvir/ paritaprevir/ ritonavir and dasabuvir (OPrD) for 8 (n=197) Vs OPrD for 12 weeks (n=574)	N=771 Follow-up: 12 weeks after end of treatment (EOT)	-Treatment naïve adults infected with HCV genotype 1b with non-advanced hepatic fibrosis	-The sustained virologic response (SVR) defined as undetectable HCV RNA at least 12 weeks after the end of treatment. -Safety	-Overall SVR rate calculated according to the intent-to-treat (ITT) analysis was achieved in 186/197 (94%) patients treated for 8 weeks and 558/574 (97%) treated for 12-weeks (p = 0.07). After exclusion of lost to follow-up patients (modified ITT (mITT) analysis), SVR rate reached 95% and 99%, respectively (p = 0.01). -Among those treated with OPrD for 12 weeks, 53 patients (9.2%) received additionally RBV, which did not improve the efficacy and even caused insignificant reduction of SVR rate compared to patients treated with OPrD without RBV in both intent-to-treat (ITT) (93% vs 98%, p=0.05) and modified ITT (mITT) analysis (96% vs 98%, p 0.29).	-The results of this retrospective study suggest a high effectiveness of 8 and 12-weeks regimens of OPrD in genotype 1b HCV infected patients with non-advanced fibrosis. A statistically significantly higher response to the 12-week OPrD therapy than the 8-week therapy among patients who completed the treatment was observed. However, the clinical significance of this difference is

Study & Level of Evidence*	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Authors Conclusions & CHC Comments
					-A comparison carried out between the patients treated for 8 or 12-weeks without RBV revealed SVR rates of 94% vs 98% (p=0.03) in ITT, and 95% vs 98% (p=0.02) in mITT analysis, respectively. -The most common were weakness/fatigue, sleep disorders, headache and pruritus. Serious AE were reported only in the 12-weeks regimen subpopulation, mainly among patients treated without RBV. There were no deaths reported.	questionable. Further research is needed to validate these results.

ITT: Intent to treat; M-ITT: modified intent to treat; SVR: sustained virologic response; RVR: rapid virologic response; EVR- early virologic response; EOT- end of therapy response; DAAs: direct-acting antivirals

***Please see Addendum for Level of Evidence ratings and definitions.**

CONTRAINDICATIONS[1-2, 4-6, 26, 33-34, 98-100, 124, 158-160, 165, 193-194, 233, 254]

All medications in this therapeutic class have a contraindication of hypersensitivity to the active ingredient or any component of the compound. The contraindications to ribavirin apply to combinations containing ribavirin.

The table below contains any unique contraindication to the individual products within this class.

Contraindication	E/G	G/P	OPR-D	PEG-2a	PEG-2b	RIB	SOF	S/V/V	V/S
Concomitant use with potent CYP3A4/5 inducers									X[2]
Concomitant use with moderate/strong CYP3A inducers and strong inducers of CYP2C8			X						X[2]
Concomitant use w/moderate/strong CYP3A4 inducers	X[6]								X[2]
Concomitant use with Strong Inhibitors of CYP2C8			X						
Concomitant use with drugs highly dependent on CYP3A4/5 for clearance			X[2]						
Any contraindication to peginterferon alfa and/or ribavirin combo apply if use concomitantly	X		X				X		
Pregnant women or men whose female partners are pregnant				X[1]	X[1]	X	X[1]		
Hemoglobinopathy				X[1]	X[1]	X[4]			
Renal function impairment (CrCl <50ml/min)					X[1]	X			
Moderate to Severe hepatic impairment			X						
Moderate to Severe hepatic impairment (Child Pugh B or C) or with any history of prior hepatic decompensation.	X	X							
Concomitant use with didanosine				X[1]		X[4]			
Hepatic decompensation (Child-Pugh >6 class B & C) in cirrhotic patients before treatment				X	X	X[3, 5]			
Hepatic decompensation (Child-Pugh ≥6) in cirrhotic CHC patients co-infected w/HIV before treatment				X		X[3, 5]			
Autoimmune hepatitis				X	X	X[3]			

Contraindication	E/G	G/P	OPR-D	PEG-2a	PEG-2b	RIB	SOF	S/V/V	V/S
With organic anion transporting polypeptides 1B1/3 inhibitors, strong inducers of CYP3a and efavirenz	X[2]								
In neonates and infants (due to benzyl alcohol)				X					
When used in combination with ribavirin, is contraindicated in patients for whom ribavirin is contraindicated									X
Concomitant use with rifampin								X	
Concomitant with atazanavir and rifampin		X							

E/G- elbasvir/grazoprevir (Zepatier®); G/P- glecaprevir/pibrentasvir (Mavyret®); **G/P**-gelcaprevir/pibrentasvir (Mavyret®); **OPR-D**- ombitasvir/paritaprevir/ritonavir-dasabuvir (Viekira® pak); **PEG-2a-** peginterferon alfa 2a (Pegasys®); **PEG-2b-** peginterferon alfa 2b (PegIntron®); **RIB-**ribavirin (various brands); **SOF-**sofosbuvir (Sovaldi®); **S/V/V-**sofosbuvir/velpatasvir/voxilaprevir (Vosevi®); **V/S-** velpatasvir/sofosbuvir (Epclusa®)

[1] When in combination with ribavirin

[2] contraindicated medications are described in drug-drug interactions section

[3] When in combination with peginterferon

[4] When Rebetol® is used in combination therapy

[5] Not listed as contraindication with Rebetol®

[6] OATP1B1/3 inhibitors that are known or expected to significantly increase grazoprevir plasma concentrations, strong CYP3A inducers, and efavirenz.

SPECIAL POPULATIONS[1-2, 4-6, 26, 33-34, 98-100, 124, 158-160, 165, 193-194, 233, 254]

Ribavirin may cause birth defects and fetal deaths; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to therapy, use two or more forms of contraception, and have monthly pregnancy tests. There is a Ribavirin Pregnancy Registry that has been established to monitor maternal and fetal outcomes of pregnancies of female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment; healthcare providers and patients are encouraged to report cases by calling 1-800-593-2214.

In an open-label trial (N=107) of young children and adolescents aged 3-17 years, the effects of peginterferon (PegIntron®, Pegasys®) plus ribavirin on growth were reported. Results suggest that weight and growth lagged when compared to a US normative population cohort, and severely inhibited growth velocity was seen in 70% while on treatment. After treatment, most patients had rebound growth/weight.

In April 2017, an FDA bulletin was released that indicated sofosbuvir (Sovaldi®) and ledipasvir/sofosbuvir (Harvoni®) had been approved as treatment for HCV in children aged 12 to 17 years. These are the first direct-acting antivirals to be approved for use in children and adolescents with HCV.[232]

In May 2018, the AASLD/IDSA added an updated to their guidelines regarding the treatment of HCV in pregnant women. According to this update, treatment during pregnancy is not recommended due to the lack of safety and efficacy data. For women of reproductive age with known HCV infection, antiviral therapy is recommended before considering pregnancy to reduce the risk of HCV transmission to the offspring.[101]

Drug	Pediatrics	Pregnancy Category	Dosage change with Renal Insufficiency	Dosage change with Hepatic Insufficiency
peginterferon alfa-2a (Pegasys®)	>5 yrs	^[10]	CrCl 30-50: 180mcg SQ QW CrCl <30 or HD: 135mcg QW	ALT ↑ baseline: 135mcg SQ QW ↑ ALT: Use contraindicated [2, 3]
peginterferon alfa-2b (Peg-Intron®)	≥ 3yrs[4]	^[10]	CrCl 30-50: ↓ dose 25% CrCl <30: ↓ dose 50% Ribavirin & CrCl<50: No use	Contraindicated[2]
ribavirin	≥5 yrs[1]	X	CrCl 30-50: Alternate doses of 200mg & 400mg CrCl <30 or HD: 200mg daily	Contraindicated[2]
sofosbuvir (Sovaldi®)	≥3 yrs	^[5]	Mild/Moderate: Not required Severe/ESRD: Not studied	Not required[8]
Combination Products				
elbasvir/grazoprevir (Zepatier®)	No	**	Not required	Mild: Not required Moderate/Severe or those with any history of hepatic decompensation: Contraindicated
glecaprevir/pibrentasvir (Mavyret®)	≥12 yrs[9]	**	Not required	Mild (Child Pugh A): Not required Moderate or Severe (Child Pugh B or C): Contraindicated
ledipasvir/sofosbuvir (Harvoni®)	≥3 yrs[6]	**	Mild/Moderate: Not required Severe/ESRD: Not studied	Not required Decompensated cirrhosis[11]

Drug	Pediatrics	Pregnancy Category	Dosage change with Renal Insufficiency	Dosage change with Hepatic Insufficiency
o/p/r with dasabuvir (Viekira® pak)	No	**	Not required	Mild: Not required Moderate-Severe: Use contraindicated
sofosbuvir/velpatasvir/ voxilaprevir (Vosevi®)	No	**	Not required[7]	Mild: Not required Moderate-Severe: Not recommended
velpatasvir/sofosbuvir (Epclusa®)	≥6 yrs	***	Mild-Moderate: Not required Severe/ESRD: Not established[7]	Not required[11]

o/p/r with dasabuvir- ombitasvir/paritaprevir/ritonavir with dasabuvir (Viekira® pak)

[1]In those with chronic hepatitis C with compensated liver disease (Child-Pugh B or C) given with interferon or peginterferon alfa-2b

[2]In patients with autoimmune hepatitis and/or hepatic decompensation in cirrhotic CHC patients before treatment

[3]If ALT continues to increase after dose decrease or if bilirubin increases [4]With combination therapy only

[5] Boceprevir, sofosbuvir, and telaprevir alone did not produce adverse effects/events in animal development studies (class B) however they must be given with ribavirin (class X)

[6] Indication for pediatric patients 3 years or older.

[7] FDA labeling revised on 11/2019: No dosage adjustment is recommended in patients with any degree of renal impairment.

[8] Safety/efficacy not established in patients with decompensated cirrhosis [9] Pediatrics ≥12 years or weighing at least 45 kg

[10] Category X when used with ribavirin due to ribavirin

[11] Clinical & hepatic lab monitoring is recommended for patient's w/decompensated cirrhosis receiving treatment with Epclusa®

[12] Pediatric patients 6 years of age and older or weighing at least 17 kg.

** No pregnancy category but risk summary indicates no human data is available for use in pregnant woman to inform a drug-associated risk, thus consider risks/benefits of use when prescribing to a pregnant woman

*** If used in combo with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant; There are no adequate human data to establish if Epclusa® poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was seen with Epclusa at exposures greater than those in humans at the recommended dose

^ No pregnancy category. No adequate/well-controlled studies in pregnant women to inform a drug-associated risk. Based on animal reproduction studies, it can cause fetal harm and should be assumed to have abortifacient potential. Combination treatment with ribavirin is contraindicated in women who are pregnant and in the male partners.

ADVERSE DRUG REACTIONS[1,2,4-6,13, 26, 33-34, 98-100, 124, 158-160, 165, 193-194, 233, 254]

All alpha interferons carry an FDA-mandated box warning concerning incidence or aggravation of fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Close patient monitoring with periodic clinical and laboratory evaluations is recommended, as is withdrawal of therapy in patients with persistently severe or worsening signs or symptoms of such conditions.

A box warning for ribavirin warns of potential birth defects and/or fetal death. In addition, ribavirin causes hemolytic anemia, with potential worsening of cardiac disease. An additional warning indicates that because ribavirin is genotoxic and mutagenic, it should be considered a potential carcinogen.

A box warning was added to Pegasys® in 2015 detailing that the medication may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor closely and withdraw therapy with persistently severe or worsening signs or symptoms of the above disorders.

A box warning was added to all of the direct-acting antiviral agents in February 2017 discussing the risk of hepatitis B virus reactivation in patients co-infected with HCV and HCB. Reactivation of HBV infection may be accompanied by hepatitis, and in severe cases, increases in bilirubin levels, liver failure, and death can occur. Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment. In patient with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment.

*** There was no placebo data to compare with for the interferon products. ****

Cardiovascular Adverse Reaction	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)	ribavirin (various)
Chest pain	-	6%	5-9%

- Event not reported.

CNS Adverse Reaction	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)	ribavirin (various)
Agitation	-	2%	5-8%
Anxiety	19%	28%	33%
Concentration impaired	8%	10%	10%
Depression	18%	29%	20%
Dizziness	16%	12%	14%
Emotional lability	-	28%	7-12%
Fatigue/asthenia	56%	52%	65%
Headache	54%	56%	43%
Insomnia	19%	23%	30%
Irritability	19%	28%	33%
Malaise	-	7%	-
Memory impaired	5%	-	6%
Mood altered	3%	-	5%
Nervousness	19%	4%	33%

- Event not reported.

Dermatologic Adverse Reaction	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)	ribavirin (various)
Alopecia	23%	22%	28%
Dermatitis	8%	-	16%
Dry skin	4%	11%	10%
Eczema	1%	-	5%
Flushing	-	6%	-
Injection site reactions *	22%	47%	23%
Pruritus	12%	12%	19%
Rash	5%	6%	8%
Sweating ↑	6%	6%	6%

- Event not reported. * Includes ecchymosis, erythema, pain

Endocrine Adverse Reaction	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)	ribavirin (various)
Hypothyroidism	3%	5%	4%

- Event not reported.

Gastrointestinal Adverse Reaction	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)	ribavirin (various)
Abdominal pain	15%	15%	8%
Anorexia	17%	20%	24%
Constipation	-	1%	-
Diarrhea	16%	18%	11%
Dry mouth	6%	6%	4%
Dyspepsia	< 1%	6%	6%
Nausea	24%	26%	25%
Vomiting	24%	7%	25%

- Event not reported.

Hematologic Adverse Reaction	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)	ribavirin (various)
Anemia	2%	0%	11
Leukopenia	-	< 1%	6-45%
Lymphopenia	3%	-	14%
Neutropenia	21%	6%	27%
Thrombocytopenia	5%	7%	5%

- Event not reported.

Hepatic Adverse Reaction	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)	ribavirin (various)
Hepatomegaly	-	6%	4%
Liver tenderness (RUQ pain)	-	8%	12%

- Event not reported.

Lab test abnormalities	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)♦	ribavirin (various)
ALT 2 x baseline	-	-	0.2-0.6%
ALT 2.1 to 5 x baseline	1%	-	1-3%
Hemoglobin 6.5 to <8g/dL	-	-	2%
Hemoglobin 8 to 9.5g/dL	-	2%	11%
Hemoglobin 9.5 to <11g/dL	17%	30%	18-32%
Neutrophils <0.5	5%	3%	5%
Neutrophils 0.5 to <0.75	-	13%	49%
Neutrophils 0.75 to <1	-	26%	49%
Neutrophils 1 to 1.5	-	35%	34%
Platelets 25 to <50 x 10^9/L	4%	4%	5%

Lab test abnormalities	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)♦	ribavirin (various)
Platelets 50 to <70 x 10^9/L	-	-	11%
Platelets 70 to 100 x 10^9/L	-	20%	5-15%
Total bilirubin 1.5 to 3mg/dL	-	10-14%	10-13%
Total bilirubin 3.1-6.0/dL	-	-	0.2-0.6%
Total bilirubin 6.1-12/dL	-	-	0.2%
Triglyceride elevation >400mg/dL	20%	-	-
Any Uric Acid ↑ (>12.1mg/dL)	-	33-38%	33-38%
WBC 1 to <1.5 x 10^9/L	-	-	1-5%
WBC 1.5 to <2 x 10^9/L	-	3%	8-24%
WBC 2 to 2.9 x 10^9/L	-	39%	38-45%

- Event not reported. ♦All column values for peginterferon alfa-2b + ribivarin in previously untreated children. [1] Reported as <8.5g/dL ; [2] Reported as <10g/dL; [3] Reported as <499/mm^3; [4] Reported as <750/mm^3; [5]Reported as 2.6xULN; [6] Reported as <50,000/mm^3

Musculoskeletal Adverse Reaction	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)	ribavirin (various)
Arthralgia	28%	23%	22%
Back Pain	9%	-	5%
Musculoskeletal disorder (unspecified)	-	-	20-28%
Myalgia	37%	54%	40%
Rigors	35%	23%	25%
Skeletal pain	-	28%	35%

- Event not reported.

Respiratory Adverse Reaction	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)	ribavirin (various)
Cough	4%	8%	10%
Dyspnea	4%	4%	13%
Pharyngitis	-	10%	12-13%
Rhinitis	-	2%	6-8%
Sinusitis	-	7%	1-14%

- Event not reported.

Miscellaneous Adverse Reaction	PEG IFN alfa-2a (Pegasys®)	PEG INF alfa-2b (Peg-Intron®)	ribavirin (various)
Abnormal/ blurred vision	4%	2%	5%
Conjunctivitis	-	4%	-
Fever	37%	22%	41%
Infection	-	11%	1-12%
Influenza-like symptoms	-	-	14-31%
Menstrual disorder	-	4%	6-7%
Pain (unspecified)	11%	6-12%	10%
RMD	10%	-	12%
Taste perversion	-	< 1%	4-9%
Weight decrease	4%	11%	10%

- Event not reported. RMD- Resistance mechanism disorders

***In the following table, the results are adjusted so that they reflect only the extent that they exceed placebo, except with Harvoni®. There was no placebo data with the Harvoni® studies. ***

Adverse Reactions	L/S[1]	E/G	G/P	o/p/r with d	SOF	S/V/V	V/S
Asthenia	-	-	-	-	-	2%	5%
Asthenia	18%	-	-	7%	-	-	
Diarrhea	3%	2%	-	-	-	4%	

Adverse Reactions	L/S[1]	E/G	G/P	o/p/r with d	SOF	S/V/V	V/S
Dyspnea	-	0%	-	-	4%	-	
Fatigue	13%	5%	11%	8%	-	7%	15%
Headache	14%	1%	13%	-	-	7%	22%
Insomnia	5%	-	-	6%	-	3%	5%
Irritability		1%	-	-	-	-	
Myalgia		-	-	-	3%	-	
Nausea	7%	5%	8%	7%	4%	6%	9%
Pruritus	-	0%	-	11%	7%	-	
Rash	-	0%	-	-	8%	-	2%
Total Bilirubin (all grades)	<1%[2]	-	3.5%[2]	-	-	-	

[4] Reported as <750/mm^3 [1] In subjects in clinical trials receiving 12 weeks of treatment [2] bilirubin elevations >1.5X UNL

- Event not reported. **L/S-** ledipasvir/sofosbuvir (Harvoni®); **E/G-** elbasvir//grazoprevir (Zepatier); **G/P-** glecaprevir/pibrentasvir (Mavyret®); **o/p/r with dasabuvir**- ombitasvir/paritaprevir/ritonavir with dasabuvir (Viekira® pak); **SOF-** sofosbuvir (Sovaldi®; **S/V/V-**sofosbuvir/velpatasvir/voxilaprevir (Vosevi®); **V/S-** velpatasvir/sofosbuvir (Epclusa®)

Placebo data was not available with velpatasvir/sofosbuvir (Epclusa®). Reported adverse events in the Astral-1 study included headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%). If Epclusa® is used in combination with ribavirin, the warnings and precautions for ribavirin apply to this combination regimen.

There have been post-marketing cases/reports of symptomatic bradycardia and cases requiring pacemaker intervention when amiodarone is used concomitantly with sofosbuvir in combination with daclatasvir or simeprevir. The co-administration of amiodarone with Epclusa® or Vosevi® is not recommended; however, for patients taking amiodarone who have no other alternative treatment options and who will be administered Epclusa® or Vosevi®. Counsel patients about the risk of symptomatic bradycardia AND Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the hear rate should occur on a daily basis through at least the first 2 weeks of treatment. Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately.

DRUG-DRUG INTERACTIONS[1-2, 4-6, 12-13, 26, 33-34, 98-100, 124, 158-160, 165, 193-194, 233, 254]

The following tables contain drug-drug interactions common to interferons as well as interactions associated with specific agents in this class.

elbasvir/grazoprevir (Zepatier®):

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Atorvastatin	↑ atorvastatin levels	Dose of atorvastatin should not exceed 20 mg
Bosentan	Decreased GRA/ELB levels	Concomitant use Contraindicated.
Carbamazepine	CYP Pathway	Concomitant use Contraindicated.
Cyclosporine		Concomitant use Contraindicated.
Fluvastatin, Lovastatin, Simvastatin	May increase statin levels	Close monitoring and lowest necessary statin dose
HIV Medications[1]	CYP Pathway	Concomitant use Contraindicated.
Ketoconazole (oral)	Increased GRA/ELB levels	Concomitant use Contraindicated.
Modafinil	CYP Pathway	Concomitant use Contraindicated.
Nafcillin	CYP Pathway	Concomitant use Contraindicated.
Phenytoin	CYP Pathway	Concomitant use Contraindicated.
Rifampin	CYP Pathway	Concomitant use Contraindicated.
Rosuvastatin	↑ levels of rosuvastatin	Dose of rosuvastatin should not exceed 10 mg
St. John's Wort	CYP Pathway	Concomitant use Contraindicated.
Tacrolimus	Increased tacrolimus levels	Frequent monitoring recommended

[1] Including Atazanavir, darunavir, efavirenz, lopinavir, saquinavir, and tipranavir

glecaprevir/pibrentasvir (Mavyret®): P-gp, breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3 inhibitors; weak CYP3A, CYP1A2, and UGT 1A1 inhibitors.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Atazanavir	↑ glecaprevir ↑ pibrentasvir	Increased risk of ALT elevations; Use is contraindicated

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Carbamazepine	↓ glecaprevir ↓ pibrentasvir	Concomitant use not recommended
Cyclosporine	↑ glecaprevir ↑ pibrentasvir	Concomitant use is not recommended in patients requiring stable doses of >100mg per day of cyclosporine
Dabigatran etexilate	↑ dabigatran	With concomitant use, refer to dabigatran's dosing modifications for P-gp inhibits with renal impairment
Darunavir, Lopinavir, or Ritonavir or containing regimens	↑ glecaprevir ↑ pibrentasvir	Concomitant use is not recommended
Digoxin	↑ digoxin	Measure serum digoxin concentrations prior to initiation – reduce digoxin dose by 50% or modify dose frequency
HMG-CoA Reductase Inhibitors	↑ Atorvastatin, Lovastatin, Simvastatin ↑ Pravastatin ↑ Rosuvastatin ↑ Fluvastatin, Pitavastatin	Atorvastatin, Lovastatin, Simvastatin: May ↑myopathy risk; concomitant use is not recommended Pravastatin: May increase myopathy risk; ↓pravastatin dose by 50% with coadministration Rosuvastatin: May increase myopathy risk; Rosuvastatin doses should not exceed 10mg Fluvastatin, Pitavastatin: May increase myopathy risk; Lowest approved dose of fluvastation or pitavastatin, if higher dose is needed, use lowest necessary dose
Inducers of P-gp/CYP3A		Decreases glecaprevir and pibrentasvir plasma concentrations
Efavirenz or efavirenz-containing regimens	↓ glecaprevir ↓ pibrentasvir	May significantly decrease plasma concentrations of glecaprevir and pibrentasvir; Concomitant use not recommended
Ethinyl estradiol-containing medications (oral contraceptives)		Concomitant use may increase risk of ALT elevations and is not recommended
Rifampin	↓ glecaprevir ↓ pibrentasvir	Decreases therapeutic effect; Concomitant use is contraindicated
St. John's Wort	↓ glecaprevir ↓ pibrentasvir	May significantly decrease plasma concentrations of glecaprevir and pibrentasvir; Concomitant use not recommended

ledipasvir/sofosbuvir (Harvoni®): Ledipasvir is an inhibitor of P-glycoprotein (P-gp). In addition, both ledipasvir and sofosbuvir are substrates of P-gp.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Amiodarone		Serious bradycardia Co-administration not recommended

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Antacids (e.g. Al/Magnesium)		Separate antacid & Harvoni® by 4 hours.
Anticonvulsants[1]		Concomitant use ↓s levels of Harvoni®; Co-administration is not recommended.
Antimycobacterials[2]		Concomitant use ↓s levels of Harvoni®; Co-administration is not recommended.
Digoxin		Monitor digoxin levels if use concomitantly w/ Harvoni®.
Elvitegravir, cobicistat, emtricitabine, tenofovir		Safety/efficacy of concomitant use not established; Co-administration not recommended.
H2 Receptor Antagonists		Doses comparable to famotidine 40mg BID can give simultaneously or 12H apart with Harvoni®.
HIV antiretrovirals[3]		Monitor for tenofovir-associated adverse reactions if administer concomitantly with Harvoni®.
HIV regimens w/ tenofovir DF & HIV PI/ritonavir[4]		Consider alternative HCV or antiretroviral therapy to avoid ↑ in tenofovir exposure.
P-gp Inducers (e.g. rifampin)		May significantly ↓ levels/therapeutic effect of Harvoni®; Concomitant use is not recommended.
PPIs		Doses comparable to omeprazole 20mg or lower can be given with Harvoni® under fasted conditions.
Rosuvastatin		May significantly ↑ rosuvastatin levels; Concomitant use not recommended.
Simeprevir		May ↑ levels of ledipasvir & simeprevir; Concomitant use not recommended.
Sofosbuvir-containing products		Concomitant use not recommended.
St. John's wort		Concomitant use not recommended.
Tipranavir/ritonavir		Concomitant use ↓s levels of Harvoni®; Co-administration is not recommended.

[1] Including carbamazepine, phenytoin, phenobarbital, oxcarbazepine [2] Including rifabutin, rifampin, rifapentine

[3] efavirenz, emtricitabine, tenofovir disoproxil fumarate (DF) [4] HIV PI- protease inhibitor/ritonavir

ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira® pak) ***Contraindications***: Ritonavir is a CYP3A4 inhibitor.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
CYP3A4 Substrates		Concomitant use contraindicated.
CYP3A4 Inducers		Concomitant use contraindicated.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Alfuzosin		Potential for hypotension; Concomitant use contraindicated.
Anticonvulsants[1]		Potential ↓ levels of hep C agents; Concomitant use contraindicated.
Cisapride		Concomitant use contraindicated.
Colchicine		Concomitant use contraindicated.
Dronedarone		Concomitant use contraindicated.
Efavirenz		Liver enzyme elevations; Concomitant use contraindicated.
Ergot derivatives		Acute ergot toxicity; Concomitant use contraindicated.
Gemfibrozil[2]		↑ in dasabuvir exposure, thus ↑ risk QT prolongation; Concomitant use contraindicated w/Viekira® pak only.
Lovastatin		Potential for myopathy; Concomitant use contraindicated.
Lurasidone		Concomitant use contraindicated.
Midazolam (PO)		↑ levels of benzodiazepines; Concomitant use contraindicated.
OCs or other ethinyl estradiol products		Potential for ALT elevations; Concomitant use contraindicated.
Pimozide		Potential for cardiac arrhythmias; Concomitant use contraindicated.
Ronolazine		Concomitant use contraindicated.
Rifampin		Potential ↓ levels of hep C agents; Concomitant use contraindicated.
Sildenafil (when used for PAH)		↑ potential for sildenafil-associated adverse events; Concomitant use contraindicated.
Simvastatin		Potential for myopathy; Concomitant use contraindicated.
St. John's wort		Potential ↓ levels of hep C agents; Concomitant use contraindicated.
Triazolam		↑ levels of benzodiazepines; Concomitant use contraindicated.

[1] Including carbamazepine, phenytoin, phenobarbital [2] Only applies to Viekira® pak/Viekira® XR

ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira® pak): Ritonavir is a CYP3A4 inhibitor.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Alprazolam		↑ alprazolam levels; Monitor and use with caution, ↓ alprazolam dose prn.
Angiotensin Receptor Blockers[2]		↓ dose of ARB and monitor for hypotension
Antiarrhythmics[1]		↑levels of antiarrhythmics; Use with caution and monitor levels.
APAP/hydrocodone		↓ hydrocodone dose by 50% and monitor.
Atazanavir/Ritonavir		Use Atazanavir 300mg w/out ritonavir QAM w/Viekira®
Buprenorphine/naloxone		Dose adjustment not required but monitor for sedative/cognitive effects.
Calcium Channel Blockers		↓ dose of CCB and monitor
Carisoprodol		Increase dose if needed
Cyclobenzaprine		Increase dose if needed
Cyclosporine		↑ cyclosporine levels; Monitor levels and adjust dose of cyclosporine.
Darunavir/Ritonavir		Concomitant use not recommended w/Viekira® pak;
Fluticasone		Concomitant use may ↓ serum cortisol levels; Use alternative corticosteroid.
Furosemide		↑ furosemide; Monitor and patient response.
Ketoconazole		Max ketoconazole dose of 200mg with concomitant use.
Lopinavir/Ritonavir		Concomitant use not recommended.
Metformin		Monitor combination.
Omeprazole		Monitor for ↓efficacy of omeprazole; Consider ↑ omeprazole dose to max 40mg/day
Pravastatin		↑ pravastatin levels; Pravastatin dose should not exceed 40mg/day.
Quetiapine		Consider alternative anti-HCV therapy to avoid ↑ in quetiapine in patients starting HCV.
Rilpivirine		Concomitant use not recommended due to potential for QT interval prolongation.
Rosuvastatin		↑ rosuvastatin levels; Rosuvastatin dose should not exceed 10mg/day.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Salmeterol		Concurrent use not recommended.
Tacrolimus		↑ tacrolimus levels; Monitor levels and adjust dose of tacrolimus.
Voriconazole		Concomitant use not recommended.

[1] Including amiodarone, bepridil, disopyramide, flecainide, lidocaine systemic, mexiletine, propafenone, quinidine

[2] Valsartan, losartan, candesartan

peginterferon alfa-2a (Pegasys®):

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Methadone	Unknown	↑ Methadone levels; Monitor combination.
Telbivudine	Unknown	May ↑ risk of telbivudine related peripheral neuropathy Safety/efficacy of combo not shown.
Theophylline	Unclear	↓ Metabolism of theophylline which raised AUC levels by 25%; Monitor combination & adjust dose prn.
Nucleoside Analogues	Unknown	Discontinuation, dose reduction, or bothshould be considered as appropriate
Zidovudine	Unknown	Combination therapy resulted in severe neutropenia and anemia more frequently. Discontinuation, dose reduction, or both should be considered as appropriate

peginterferon alfa-2b (PegIntron®):

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
CYP2C8/9 Substrates [High risk]	peginterferon alfa-2b on CYP2C9 substrate	↓ Serum concentration of CYP2C9 substrate; Monitor combination.
CYP2D6 substrates	peginterferon alfa-2b on CYP2D6 substrate	↓ Serum concentration of CYP2D6 substrate; Monitor combination.
Immunosuppresants[1]		Effect unknown Monitor combination
Methadone	Unknown	↑ Methadone levels; Monitor combination.
Telbivudine	Unknown	May ↑ risk of telbivudine related peripheral neuropathy Safety/efficacy of combo not shown.
Theophylline		↑ Theophylline levels Monitor combination
Thioridazine		↑ Thioridazine levels Monitor combination

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Zidovudine		Monitor combination

[1] Including cyclosporine, sirolimus, tacrolimus

ribavirin (Rebetol®, Ribasphere®):

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Nucleoside reverse transcriptase inhibitors (NRTI)	Not reported	↑ Hepatotoxic effect of reverse transcriptase inhibitor; Consider therapy modification. *Didanosine: use is contraindicated.*
Azathioprine	Inhibition of azathioprine metabolism by ribavirin	↑ azathioprine metabolites; Monitor therapy with CBC.

sofosbuvir (Sovaldi®):

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Amiodarone		Concomitant use not recommended; if coadministration is required, cardiac monitoring is required
Anticonvulsants[1]	↓ sofosbuvir	Concomitant use not recommended.
Antimycobacterials[2]	↓ sofosbuvir	Concomitant use not recommended.
Herbal supplements (St. John's wort)	↓ sofosbuvir	Concomitant use not recommended.
HIV Protease Inhibitors (tipranavir/ritonavir)	↓ sofosbuvir	Concomitant use not recommended.

[1] Includes carbamazepine, phenytoin, phenobarbital, and oxcarbazepine [2] Includes rifabutin, rifampin, and rifapentine

sofosbuvir/velpatasvir/voxilaprevir (Vosevi®): All 3 components are P-gp and BCRP substrates. Voxilaprevir is also an OATP1B1 and OATP1B3 substrate. Velpatasvir has shown slow metabolic turnover, in vitro, by CYP2B6, CYP2C8, and CYP3A4, as well as voxilaprevir for CYP1A2, CYP2C8, and primarily CYP3A4.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Amiodarone	Unknown	Concomitant use not recommended; if coadministration is required, cardiac monitoring is required
Antacids	↓ velpatasvir	Separate administration by 4 hours
Anticonvulsants[2]	↓ sofosbuvir, velpatasvir, voxilaprevir	Concomitant use not recommended
Antimycobacterial	↓ sofosbuvir, velpatasvir, voxilaprevir (single dose) ↑ voxilaprevir (multiple doses)	Rifampin contraindicated; Rifabutin/rifapentine not recommended

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
BCRP substrates[1]		Concomitant use not recommended
Cyclosporine	↑ voxilaprevir	Concomitant use not recommended
Dabigatran	↑ dabigatran	Clinical monitoring of dabigatran & adjust dose prn in setting of moderate renal impairment
Digoxin	↑ digoxin	Monitor digoxin levels & adjust digoxin dose prn
Herbal supplements (St. John's wort)	↓ sofosbuvir, voxilaprevir, velpatasvir	Concomitant use not recommended.
H2 antagonists	↓ velpatasvir	Do not exceed doses comparable with famotidine 40mg BID
HIV Protease Inhibitor[3]	Atazanavir, lopinavir: ↑ voxilaprevir Tipranavir/ritonavir: ↓ sofosbuvir, velpatasvir Efavirenz: ↓ voxilaprevir, velpatasvir Tenofovir DF: ↑ tenofovir	Concomitant use not recommended.
HMG-CoA Reductase Inhibitors	↑ statin levels	Not recommended: rosuvastatin, pitavastatin Adjust dose: max pravastatin 40mg QD Others: Use lowest approved statin dose
Inducers of P-gp		Concomitant use not recommended
Moderate-Potent inducers of CYP2B6, CYP2C8, or CYP3A4		Concomitant use not recommended
Proton pump inhibitors	↓ velpatasvir	Omeprazole 20mg has been studied & can be used concomitantly, but other PPIS have not been studied.

[1] e.g. methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan
[2] carbamazepine, phenytoin, phenobarbital, oxcarbazepine [3]atazanavir- or lopinavir-containing regimens, tipranavir/ritonavir, and efavirenz

velpatasvir/sofosbuvir (Epclusa®):

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Amiodarone		Concomitant use not recommended; if coadministration is required, cardiac monitoring is required
Antacids	↓ velpatasvir	Separate Epclusa® and antacid by 4 hours
Anticonvulsants[1]	↓ sofosbuvir, velpatasvir	Concomitant use not recommended.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Antimycobacterials[2]		Concomitant use not recommended.
Atorvastatin		Concomitant use ↑ levels of atorvastatin; Monitor adverse reactions (myopathy, rhabdomyolysis)
Digoxin	↑ digoxin	Monitoring of digoxin levels is recommended
Efavirenz or efavirenz-containing regimens	↓ velpatasvir	Concomitant use not recommended
H2-receptor antagonists (e.g. famotidine)	↓ velpatasvir	May be given together with or 12 hours apart from Epclusa® at a dose that does not exceed doses comparable to famotidine 40mg BID
Proton-pump inhibitors	↓ velpatasvir	Concomitant use not recommended; if medically necessary, take Epclusa® with food & take 4 hours before omeprazole 20mg. Use w/other PPIs not studied.
Regimens containing tenofovir DF	↑ tenofovir	Monitor for tenofovir-associated adverse reactions
Rosuvastatin		If use concomitantly, do not exceed 10mg rosuvastatin
St. John's wort	↓ sofosbuvir, velpatasvir	Concomitant use not recommended
Tipranavir/ritonavir	↓ sofosbuvir, velpatasvir	Concomitant use not recommended
Topotecan		Concomitant use not recommended

[1] Includes carbamazepine, phenytoin, phenobarbital, and oxcarbazepine [2] Includes rifabutin, rifampin, and rifapentine

GUIDELINES

In 2012, Ramachandran et al[78] published consensus guidelines for the use of protease inhibitors in genotype 1 chronic hepatitis infected patients in the UK. After review of published literature, protease inhibitor therapy should be considered for all genotype 1 chronic HCV patients including treatment naïve and patients with virologic failure after previous standard of care therapy. Non-genotype 1 patients should be treated without protease inhibitors and according to previous standards of care. Protease inhibitor therapy cannot be recommended for patients with decompensated liver disease, hepatitis B co-infection, active cancer or post-transplant due to limited data in these patients. Caution should be used in patients with neutropenia, thrombocytopenia, or anemia, as well as those patients that may have serious and significant drug interactions with protease inhibitor therapy. Either formulation of peginterferon alfa can be used with boceprevir or telaprevir. Response guided boceprevir and telaprevir are suggested for those patients with detectable HCV RNA after 4 weeks of lead in peginterferon or in those patients whom lead in therapy is not used. Full treatment courses of boceprevir or telaprevir are suggested for those patients with cirrhosis. Stop points for therapy should be consistent with other definitions of non-response.

In 2018, the Department of Veterans Affairs and the National Hepatitis C Program Office published updated guidelines on the management and treatment of hepatitis C virus infection.[96, 350] An extensive review of published data recommends all patients with chronic HCV infection should be evaluated for HCV antiviral treatment. Patients being considered for HCV therapy should receive pretreatment assessments. Patients should also be counseled on the likelihood of achieving SVR before initiating therapy. Treatment should be provided to those individuals who meet criteria and who are at greatest risk for progressive liver disease. These guidelines provide therapy protocols for both treatment-naïve and treatment-experienced patients with HCV genotypes 1, 2, 3 and 4. Additional guidance is provided on groups with special considerations for treatment such as mental health disorders, substance or alcohol use disorders, HIV/HCV coinfection, and modifications for drug use in patients with renal or hepatic impairment. Many of these patients will have relative contraindications to treatment because of concomitant psychiatric disease or other comorbid conditions. Because of these barriers, close collaboration is necessary with specialists, including psychiatrists and substance abuse providers.

In April 2016, the World Health Organization[230] updated their Guidelines for the Screening, Care, and Treatment of Persons with Chronic Hepatitis C Infection. The objectives of the WHO guidelines are to provide updated evidence-based recommendations for the treatment of persons with HCV infection using, where possible, all DAA-only combinations. The guidelines also provide recommendations on the preferred regimens based on patient's HCV genotype and clinical history and assess the appropriateness of continued use of certain medications. WHO recommends that DAA regimens be used for the treatment of persons with Hepatitis C infection rather than regimens with pegylated interferon and ribavirin. However, in patients with HCV GT 3 infection with cirrhosis or patients with GT5 or 6 infections, an interferon-based regimen like sofosbuvir/pegylated-interferon and ribavirin is still recommended as an alternative treatment option. A complete summary of their recommendations can be found on the WHO website: http://www.who.int/hepatitis/en/. Additionally, in April 2017, the WHO published its first Global Hepatitis report with the intent of tracking process for implementing a new global strategy against HCV, the road to elimination by 2030-full report: http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1.

In 2018, the European Association for the Study of Liver (EASL)[326] released their updated recommendations on the treatment of Hepatitis C two years after the prior update. The recommendations have been prepared by a panel of experts chosen by the Governing Board and are based on evidence from existing publications and presentations at international meetings, and if evidence was unavailable, the experts' personal experiences and opinions. The recommendations are based on currently licensed medications and are updated regularly following approval of new drug regimens by the European Medicines Agency. These guidelines can be found at: https://www.easl.eu/.

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA)[101] collaboratively developed this guidance with hepatology and infectious disease experts for Recommendations for Testing, Managing, and Treating Hepatitis C. These evidence-based recommendations are updated frequently, last updated in December 2019, as data becomes available in this rapidly evolving therapeutic area. They include a thorough review of the evidence and outline the treatment recommendations in detail by genotype, as well as other factors, such as prior treatment status and HIV status. This well-respected, evidence-based review does include use of some drugs based on available

evidence outside of the FDA labeled indications. This guidance document is frequently updated and available at: http://www.hcvguidelines.org.

SUMMARY

There is no effective vaccine against hepatitis C, therefore primary prevention of HCV infection consists of reducing the risk of exposure in health care settings and in high risk populations such as people who inject drugs.[264] The therapy for chronic hepatitis C has evolved steadily since alfa interferon was first approved for use numerous years ago. The standard for treatment until 2014 was a treatment length guided by patient factors such as previous treatment and response to therapy with a protease inhibitor combined with a pegylated interferon. Addition of a large inert polyethylene glycol (PEG) molecule changed the uptake, distribution and excretion of interferon and prolonged its half-life. Because of its ease of administration and superior efficacy, peginterferon replaced standard interferon as a component of combination therapy for hepatitis C.

Ribavirin monotherapy has little effect on Hepatitis C virus alone, but when combined with interferon, the sustained viral response (SVR) increases two to three-fold. Of note, genotype 1 infected patients had only a 40-55% sustained viral response to combination interferon-ribavirin treatment, whereas genotypes 2 and 3 had a 70-80% sustained viral response to this same treatment.[18]

The serious nature and the frequency of hepatitis C in the population made the search for new therapies of prime importance. New, direct-acting antivirals have become a reality, and more are in development, notably specific inhibitors of HCV-derived enzymes such as protease, helicase, and polymerase inhibitors. Nonspecific cytoprotective agents might also be helpful by blocking the cell injury caused by the HCV infection. Molecular approaches are likewise worthy of investigation; these consist of using ribozymes, which are enzymes that break down specific viral RNA molecules, and antisense oligonucleotides, which are small complementary segments of DNA that bind to viral RNA and thereby inhibit viral replication.

Published studies suggested that the first protease inhibitors given in combination with peg-interferon and ribavirin significantly improved sustained virologic response (SVR) rates in both treatment naïve and previously treated patients.[46-51] These agents represented a significant advance in the treatment of hepatitis C improving typical SVR rates by 10% or greater when added to pegylated interferon and ribavirin therapy. However, these earlier agents still required co-administration with interferon and remained difficult to tolerate over lengthy regimens. Both telaprevir (Incivek®) and boceprevir (Victrelis®) have been removed from the market.

Several studies published in 2013 with sofosbuvir (Sovaldi®)-based regimens (a nucleotide analog polymerase inhibitor) demonstrated high rates of sustained virologic response against chronic hepatitis C genotypes 1, 2, 3, and 4 in a variety of patient populations including treatment-naïve, those who did not have a response to prior interferon treatment, and those who had a contraindication to interferon.[106-109] Based largely upon this evidence, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America began recommending sofosbuvir (Sovaldi®) as a component of an antiviral regimen for treatment of HCV genotypes 1, 2, 3 or 4 infection.[101] Numerous studies published in 2014 through present time demonstrated the significant improvement in SVRs associated with the combination

drug sofosbuvir/ledipasvir (Harvoni®). In one trial by Bourliere et al[139] there was no statistically significant difference in SVR12 between the sofosbuvir/ledipasvir group with ribavirin when compared with the group given sofosbuvir/ledipasvir without ribavirin. These groups achieved SVR12 in 97% and 95% of patients respectively. These SVR rates were significantly improved compared to the prior standard of care using peginterferons and ribavirin and rates of adverse events were significantly decreased.

In 2014, an additional treatment option for genotype 1 patients was approved consisting of the combination of ombitasvir, paritaprevir and ritonavir co-packaged with dasabuvir (Viekira Pak®). In 2015, daclatasvir (Daklinza®) was approved for genotype 1 and 3 patients and the combination drugs used in Viekira® Pak without co-packaged dasabuvir (Technivie®) also became available for use in patients with genotype 4 infection. (However, Daklinza®, Viekira® XR and Technivie® have been discontinued from the manufacturer and are no longer available). Elbasvir/grazoprevir (Zepatier®) was approved in 2015 for chronic HCV genotypes 1 or 4 with or without ribavirin. Velpatasvir/sofosbuvir (Epclusa®) was FDA approved in 2016 for chronic HCV genotype 1, 2, 3, 4, 5, and 6 infections. These products may be taken with or without ribavirin.[101] These new regimens usually have a short treatment duration (usually 12 weeks), are easy to administer (as few as one pill/day), are very effective (SVR rate of >90%) and are well tolerated with few adverse events.[230]

In 2017, the FDA released a box warning for all of the direct-acting antiviral agents discussing the risk of hepatitis B reactivation in patients who are on these medications and who are co-infected with HBV and HCV. It is important before intiating any of these therapies to measure HBsAg and anti-HBc to search for evidence of current or prior HBV infection. In patients with serologic evidence of HBV, make sure to monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment. Reactivation of HBV could cause in severe cases increases in bilirubin levels, liver failure, and death.[159]

In 2017, the FDA approved Vosevi®, a combination of two previously approved drugs, sofosbuvir and velpatasvir, and a new drug voxilaprevir for the treatment of adults with chronic hepatitis C virus genotypes 1 through 6 without cirrhosis or with mild cirrhosis. Vosevi® is the first treatment approved for patients previously treated with the direct-acting antiviral drug sofosbuvir or other NS5A inhibitors.[233]

In April 2017, an FDA bulletin was released that indicated sofosbuvir (Sovaldi®) and ledipasvir/sofosbuvir (Harvoni®) had been approved as treatment for HCV in children aged 12 to 17 years. These were the first direct-acting antivirals to be approved for use in children and adolescents with HCV.[232] In 2020, the FDA further expanded the labeled indication of sofosbuvir (Sovaldi®) and ledipasvir/sofosbuvir (Harvoni®) to children ≥ 3 years of age. Also, in 2020, the FDA expanded the labeled indication of velpatasvir/sofosbuvir (Epclusa®) to include children ≥ 6 years of age.

In 2017 the FDA approved Mavyret®, a combination of glecaprevir and pibrentasvir, for the treatment of adults with chronic hepatitis C virus genotypes 1 through 6 without cirrhosis or with mild cirrhosis. Mavyret® may also be used in patients with moderate to severe kidney disease, including dialysis. Mavyret® is the first treatment approved for eight weeks duration in treatment-naïve patients without cirrhosis compared to the standard treatment duration of twelve weeks.[254] In 2018, the Mavyret® package insert was updated to include recommendation for use in liver and kidney transplant recipients. In 2019, further additions were made to the Mavyret® package insert which included another update to the liver and kidney transplant recipients as well as new patient populations. Pediatric patients over the age of 12 years who weigh at least

45 kg were added for HCV genotypes 1 through 6 without cirrhosis or with compensated cirrhosis as well as those with HCV genotype 1 who had previously been treated with a regimen containing a HCV NS5A inhibitor or an NS3/4A protease inhibitor (but not both). The update to the liver and kidney transplant recipient indication also included this pediatric population over the age of 12 years who weigh at least 45 kg.

The IDSA/AASLD guidelines are considered a "living document" with changes made online as frequently as new information becomes available.[101] The current guideline contains a recommendation that all patients chronically infected with hepatitis C be offered treatment unless they have a limited life expectancy, although they continue to discuss that certain individuals are at a higher risk of disease related complications (e.g. HIV infection, advanced fibrosis). It is anticipated that these guidelines will continue to be amended as new drugs and new information becomes available.

Presently, the best means of preventing new cases of this disease consists of treating those currently infected, screening the blood supply, encouraging health professionals to take precautions when handling blood and body fluids, and informing people about high-risk behaviors. Programs to promote needle exchange may offer some hope of decreasing the spread of hepatitis C among injection drug users. In addition, all drug users should receive instruction in safer injection techniques. A meta-analysis conducted by Zanini[65] suggests that a multi-disciplinary approach to hepatitis C therapy with an addiction specialist may offer improved benefits. Also, Veterans Affairs guidelines recommend multidisciplinary teams, such as psychiatrists or substance abuse providers, be used to optimally manage hepatitis C and associated comorbities.[96,350]

While the newer agents to treat HCV offer clear advantages in both efficacy and tolerability over older therapies, the determination of the most cost-effective therapy and the timing of therapy relative to disease stage will remain areas of active discussion and study. Factors such as genotype, prior treatments, and degree of liver fibrosis remain key factors to consider. When several drugs offer very high rates of treatment efficacy (SVR cure rates) with similar tolerability and treatment course length, comparative cost can be a reasonable factor to consider.

ADDENDUM

Change Healthcare Levels of Evidence	
Level of Evidence	**Criteria**

1a	• Systematic review or meta-analysis of high-quality studies
	  ○ Patient-oriented outcomes (mortality, morbidity, symptom improvement, quality of life)
	• High quality randomized controlled trial
	  ○ Patient-oriented outcomes (mortality, morbidity, symptom improvement, quality of life)
	  ○ Double-Blinded
	  ○ Clearly defined appropriate endpoints
	  ○ Intent-to-treat analysis in primary group, appropriate use of per protocol population if utilized
	  ○ Appropriate handling of dropouts (e.g. LOCF, MMRM)

1b	• Systematic review or meta-analysis of high-quality studies
	  ○ Disease-oriented outcomes (physiologic or surrogate end points)
	• High quality randomized controlled trial
	  ○ Disease-oriented outcomes (physiologic or surrogate end points)
	  ○ Double-Blinded
	  ○ Clearly defined appropriate endpoints
	  ○ Intent-to-Treat analysis in primary group, appropriate use of per protocol population if utilized
	  ○ Appropriate handling of dropouts (e.g. LOCF, MMRM)

2	• Low quality randomized controlled trial
	  ○ Clearly defined primary outcome
	  ○ Open label (non-blinded)
	  ○ Appropriate handling of dropouts (e.g. LOCF, MMRM)
	• Non-randomized controlled trial
	• Cohort study

3	• Case control study/Case series/expert opinion

Definitions

Intent-to-Treat: Inclusion of all subjects who received at least one dose of study medication or placebo

Last Observation Carried Forward (LOCF): Method of handling drop-outs wherein the last measurement is utilized as the final outcome data point at study conclusion.

Mixed Model Repeated Measures (MMRM): A statistical model to handle dropouts. Uses repeated measures to define data point outcome trends.

Observed Cases: Method of handling drop-outs, which only includes study completers.

Per-Protocol population: A sub-group of intention to treat population often used to enrich for compliance.

Number Needed to Treat (NNT): The number of subjects required to bring about one response on the primary outcome.

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