2014

AN IAS–USA STATE-OF-THE-ART CLINICAL CONFERENCE ON THE MANAGEMENT OF HEPATITIS C VIRUS IN THE NEW ERA: SMALL MOLECULES BRING BIG CHANGES

HEPATITIS C VIRUS (HCV) INFECTION: LOOKING BEYOND THE INTERFERON ALFA ERA

Monday, October 13, 2014
Gleacher Center
Chicago, Illinois

CO-CHAIRS
Donald M. Jensen, MD
Professor of Medicine
Director, Center for Liver Diseases
University of Chicago Medical Center
Chicago, Illinois

Kenneth E. Sherman, MD, PhD
Gould Professor of Medicine
Director, Division of Digestive Diseases
University of Cincinnati College of Medicine
Cincinnati, Ohio

CME Credits
The International Antiviral Society–USA (IAS–USA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The IAS–USA designates this live activity for a maximum of 6.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nursing Credits
Education Review Systems is an approved approver of continuing nursing education by the Alabama State Nursing Association, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation. Provider # 5-115. This program is approved for 6 hours of continuing nursing education.

Educational Review Systems is also approved for nursing continuing education by the state of California, the state of Florida and the District of Columbia.

Pharmacy Credits
Educational Review Systems is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education. This program is approved for 6 hours (0.6 CEUs) of continuing pharmacy education credit. Proof of participation will be posted to your NABP CPE profile within 4 to 6 weeks to participants who have successfully completed the post-test. Participants must participate in the entire presentation and complete the course evaluation to receive continuing pharmacy education credit.

ACPE # 0761-9999-14-271-L02-P

E-mail: registration@iasusa.org
Follow us on Twitter
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Register Now!
IAS–USA Monthly Webinar Series
www.iasusa.org/webinars

The Psychiatry of AIDS:
A Guide to Diagnosis and Treatment
Glenn J. Treisman, MD, PhD
Thursday, December 11, 2014
1:00 PM (ET)
www.iasusa.org/content/psychiatry-aids-guide-diagnosis-and-treatment-webinar-2014

There is no charge to participate.

This activity has been approved for AMA PRA Category 1 Credit™.
This activity is eligible for ANCC credit, see final CNE activity announcement for specific details.
This activity is eligible for ACPE credit, see final CPE activity announcement for specific details.
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**Please note:** The case-based presentation slides are intentionally omitted from the course materials so that the case discussions can be spontaneous. Electronic copies of the cases will be available to all participants following the course.
The IAS–USA

The mission of the IAS–USA is to improve the treatment, care, and quality of life for people with HIV, hepatitis C virus, or other viral infections through high-quality, relevant, balanced, and needs-oriented education and information for practitioners who are actively involved in medical care. The educational activities are particularly intended to bridge clinical research and patient care.

Members of the Viral Hepatitis Advisory Board serve in a volunteer capacity and are not compensated for their roles in oversight and governance of the viral hepatitis educational efforts. As part of its duties, the Advisory Board oversees the needs assessment, design, development, and evaluation of all viral hepatitis educational activities.

Viral Hepatitis Advisory Board

**Raymond T. Chung, MD**  
Associate Professor of Medicine  
Harvard Medical School  
Director of Hepatology  
Vice Chief of Gastroenterology  
Massachusetts General Hospital  
Boston, Massachusetts

**Douglas T. Dieterich, MD, FACP**  
Professor of Medicine  
Director of Continuing Medical Education  
Mount Sinai School of Medicine  
New York, New York

**Charles W. Flexner, MD**  
Professor of Medicine, Pharmacology, and International Health  
Associate Director  
Graduate Training Program in Clinical Investigation  
The Johns Hopkins University  
School of Medicine  
Baltimore, Maryland

**Marshall J. Glesby, MD, PhD**  
Professor of Medicine and Public Health  
Associate Chief, Division of Infectious Diseases  
Medical Director, Cornell HIV Clinical Trials Unit  
Weill Cornell Medical College  
New York, New York

**Susanna Naggie, MD, MHS**  
Assistant Professor of Medicine  
Duke Clinical Research Institute  
Durham Veterans Affairs Medical Center  
Durham, North Carolina

**Marion G. Peters, MD**  
John V. Carbone, MD, Endowed Chair  
Professor of Medicine  
Chief of Hepatology Research  
University of California San Francisco  
San Francisco, California

**Michael S. Saag, MD**  
Professor of Medicine  
Jim Straley Chair in AIDS Research  
Director, Center for AIDS Research  
University of Alabama at Birmingham  
Birmingham, Alabama

**Robert T. Schooley, MD**  
Professor and Vice Chair of Medicine  
Head, Division of Infectious Diseases  
University of California San Diego  
La Jolla, California

**Kenneth E. Sherman, MD, PhD**  
Gould Professor of Medicine  
Director, Division of Digestive Diseases  
University of Cincinnati College of Medicine  
Cincinnati, Ohio

**David L. Thomas, MD, MPH**  
Professor of Medicine  
The Johns Hopkins Medical Institutions  
Baltimore, Maryland

**David L. Wyles, MD**  
Associate Professor of Medicine  
University of California San Diego  
La Jolla, California
Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes

- **Hepatitis C Virus Infection: Looking Beyond the Interferon Alfa Era.** This full-day advanced CME course series is designed for clinicians who are experts in the complexities of antiretroviral management and who are well positioned to join their hepatology and gastroenterology colleagues in providing care for HCV-infected patients, in what has become an exciting new era in HCV care. Visit www.iasusa.org/attend for upcoming courses.

- **Half-Day Intensive Workshops on Evolving Strategies in Viral Hepatitis Management.** This small-group, intensive, interactive, case-based workshop series is designed to address current management options for viral hepatitis infections, particularly with the most recent and emerging treatments for HCV infection. Attendees will learn from experts, discuss their own clinical cases, and contribute their own expertise. Attendance is limited to 35 clinical decision makers.

Conference on Retroviruses and Opportunistic Infections (CROI)

The CROI Foundation has partnered with the IAS–USA to sponsor the Conference.


Topics in Antiviral Medicine™

The IAS–USA publishes the peer-reviewed journal, *Topics in Antiviral Medicine*,™ 4 to 6 times a year as a scientific resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV or other viral infections. The journal offers CME credit and is indexed on Index Medicus/MEDLINE. To be added to our mailing list, please create an account on the IAS–USA website at www.iasusa.org. See FAQ page for additional information on how to create an account. Subscriptions are complimentary and are available in electronic format.

Treatment and Testing Guidelines

The IAS–USA sponsors the development of clinical practice guidelines. The guidelines are written by independent panels of researchers and clinicians from around the world and focus on management issues for which definitive evidence is lacking. Guidelines for viral load testing, antiretroviral therapy, HIV drug resistance testing, cytomegalovirus (CMV) infection, and metabolic complications have been published.


Recommendations for Testing, Managing, and Treating Hepatitis C

The IAS–USA serves as the collaborating partner for the AASLD/IDSA/IAS–USA HCV Guidance and is responsible for providing expertise and administrative support to HCV Guidance Panel members and processes. A representative from the IAS–USA serves as a co-chair of the HCV Guidance Panel, and other representatives of the IAS–USA with expertise in the field of HCV infection in adults serve as Panel members. Information about the HCV Guidance can be found at www.HCVguidelines.org.
Drug Resistance Mutations Projects

- **HIV**: Through the HIV Drug Resistance Mutations Panel, the IAS–USA provides regular updates on the mutations associated with resistance to antiretroviral drugs. The information on relevant mutations is collected and reviewed by a panel of acknowledged leaders in the field. This information is available in *Topics in Antiviral Medicine*,™ on pocket-reference cards (available from the IAS–USA), and on the IAS–USA website at [www.iasusa.org](http://www.iasusa.org).

- **HCV**: The IAS–USA has published information on mutations in HCV that impact susceptibility to HCV drugs approved by the US Food and Drug Administration (FDA) and to investigational drugs. This information, last updated in January 2013, is available in *Topics in Antiviral Medicine*,™ and on the IAS–USA website at [www.iasusa.org](http://www.iasusa.org).

**Improving the Management of HIV Disease®**

**Live CME Courses**

These annual, full-day, advanced, live continuing medical education (CME) courses continue to focus on cutting-edge, scientifically rigorous issues presented by leading experts in the field of HIV medicine, providing the latest insights and data on the full spectrum of HIV- and AIDS-related treatment issues. Our live CME courses promote interaction between faculty and attendees via an audience-response touchpad system, discussion periods, and question-and-answer periods.

**Cases on the Web**

*Cases on the Web* *(COWs)* are a series of case-driven internet-based enduring material CME activities sponsored by the IAS–USA to offer physicians convenient online access to top-quality education. The *COW* program provides basic and advanced level educational activities that are offered for CME credit for as long as each *COW* is active, after which time they remain available in the *COW* archive for reference use only. Visit [www.iasusa.org/cow](http://www.iasusa.org/cow) for a current list of *COW* activities.

**Webinars**

The IAS–USA sponsors monthly CME webinars for health care practitioners. Each webinar lasts 60 to 90 minutes and will address a current topic in HIV and HCV care. For information about upcoming webinars, please visit [www.iasusa.org/webinars](http://www.iasusa.org/webinars).

**Webcasts**

IAS–USA webcasts are recordings from our popular, regional, advanced-level CME courses on HIV/AIDS- and viral hepatitis-related treatment issues. These webcasts enable clinicians who are unable to attend the live courses, including clinicians located around the world, to access clinically relevant information and learn at their own pace. These activities have been approved for *AMA PRA Category 1 Credit*.™ Visit [www.iasusa.org/webcasts](http://www.iasusa.org/webcasts) for a list of available webcasts.

**Podcasts**

Some past IAS–USA live CME courses are available as podcasts and may be downloaded from the IAS–USA website. Visit [www.iasusa.org/resources/podcasts](http://www.iasusa.org/resources/podcasts) for details and a list of available presentations. Please note that these podcasts do not offer CME credit.

**Key Slides**

The IAS–USA offers a collection of downloadable key slides from presentations at conferences or past IAS–USA live courses. Presenters have selected the slides they consider are the most informative and relevant. Key slides may be downloaded as PowerPoint files from the IAS–USA website at [www.iasusa.org/resources/slides](http://www.iasusa.org/resources/slides).

For information about any of these programs, please contact the IAS–USA.

Phone: (415) 544-9400 • Fax: (415) 544-9401

E-mail: registration*at*iasusa.org • Website: [www.iasusa.org](http://www.iasusa.org)
Course Faculty and Disclosure

In the interest of maintaining the independence of its CME activities, and in accordance with the policies of the Accreditation Council for Continuing Medical Education (ACCME), the IAS–USA requires all persons with control of content (ie, course faculty, IAS–USA Board members, and program staff; see page 12) to disclose any financial relationships that they or their spouses or partners have had with commercial companies within the past 12 months. Any real or apparent conflicts of interest of those parties are resolved prior to the CME activity being delivered. Individuals who refuse to disclose financial interests may not participate in an IAS–USA CME activity. Below are the financial interests that faculty members of this course have had within the past 12 months as of the date listed.

CHAIRS

Donald M. Jensen, MD
Professor of Medicine
Director, Center for Liver Diseases
University of Chicago Medical Center
Chicago, Illinois

Dr Jensen has received clinical research support from AbbVie, Boehringer Ingelheim Pharmaceuticals, Inc, Bristol-Myers Squibb, Genentech, Janssen Therapeutics, and Merck & Co, Inc. (Updated 10/8/14)

As a volunteer co-chair of the AASLD/IDSA/IAS–USA Hepatitis Guidance effort, Dr Jensen has divested himself of any personal financial relationships with commercial entities as of October 2013. (See www.HCVguidelines.org/node/63#methodspanel)

Kenneth E. Sherman, MD, PhD
Gould Professor of Medicine
Director, Division of Digestive Diseases
University of Cincinnati College of Medicine
Cincinnati, Ohio

Dr Sherman has received research grants or contracts awarded to his institution from AbbVie, Bristol-Myers Squibb, Genentech, Gilead Sciences, Inc, and Vertex Pharmaceuticals, Inc, and has served as an advisory board member or consultant to Merck & Co, Inc, MedImmune, Janssen Therapeutics (formerly Tibotec), and Synteract. (Updated 10/8/14)

As a volunteer co-chair of the AASLD/IDSA/IAS–USA Hepatitis Guidance effort, Dr Sherman has divested himself of any personal financial relationships with commercial entities as of October 2013. (See www.HCVguidelines.org/node/63#methodspanel)

SPEAKERS

Andrew Aronsohn, MD
Assistant Professor of Medicine
University of Chicago Medical Center
Chicago, Illinois

Dr Aronsohn has no relevant financial affiliations to disclose. (Updated 10/8/14)

As a volunteer co-chair of the AASLD/IDSA/IAS–USA Hepatitis Guidance effort, Dr Aronsohn has divested himself of any personal financial relationships with commercial entities as of October 2013. (See www.HCVguidelines.org/node/63#methodspanel)

Lucas A. Hill, PharmD
Ambulatory Care Pharmacist
University of California San Diego
San Diego, California

Dr Hill has no relevant financial affiliations to disclose. (Updated 10/8/14)

David L. Wyles, MD
Associate Professor of Medicine
University of California San Diego
La Jolla, California

Dr Wyles has received research grants awarded to the University of California San Diego from AbbVie, Gilead Sciences, Inc, Merck & Co, Inc, and Vertex Pharmaceuticals, Inc. He also served as a consultant to AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Inc, and Merck & Co, Inc. (Updated 10/8/14)

As a volunteer co-chair of the AASLD/IDSA/IAS–USA Hepatitis Guidance effort, Dr Wyles has divested himself of any personal financial relationships with commercial entities as of October 2013. (See www.HCVguidelines.org/node/63#methodspanel)
## Morning Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker/Institution</th>
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<tbody>
<tr>
<td>8:00 – 8:15 AM</td>
<td>Hepatitis C Virus Infection (HCV): Looking Beyond the Interferon Alfa Era</td>
<td>Donald M. Jensen, MD&lt;br&gt;Professor of Medicine&lt;br&gt;University of Chicago Medical Center&lt;br&gt;Kenneth E. Sherman, MD, PhD&lt;br&gt;Gould Professor of Medicine&lt;br&gt;University of Cincinnati College of Medicine</td>
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<tr>
<td>8:15 – 8:45 AM</td>
<td>Hepatitis C 101: The Basics</td>
<td>Donald M. Jensen, MD</td>
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<tr>
<td>8:45 – 8:55 AM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>8:55 – 9:25 AM</td>
<td>HCV is a LIVER Disease</td>
<td>Kenneth E. Sherman, MD, PhD</td>
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<td>9:25 – 9:35 AM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>9:35 – 10:05 AM</td>
<td>Hepatitis C Infection: Current Therapy</td>
<td>Donald M. Jensen, MD</td>
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<tr>
<td>10:05 – 10:15 AM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>10:15 – 10:35 AM</td>
<td>Break</td>
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<tr>
<td>10:35 – 11:05 AM</td>
<td>Future Therapies for HCV: What Is Coming in the Next 6 Months?</td>
<td>Andrew Aronsohn, MD&lt;br&gt;Assistant Professor of Medicine&lt;br&gt;University of Chicago Medical Center</td>
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<tr>
<td>11:05 AM – 11:15 AM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>11:15 – 11:45 AM</td>
<td>Strategies for Treating HCV Infection in HCV/HIV-Coinfected Patients</td>
<td>David L. Wyles, MD&lt;br&gt;Associate Professor of Medicine&lt;br&gt;University of California San Diego</td>
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<tr>
<td>11:45 – 11:55 AM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>11:55 AM – 12:55 PM</td>
<td>Lunch</td>
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## Afternoon Agenda

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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker/Institution</th>
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<tbody>
<tr>
<td>12:55 – 1:25 PM</td>
<td>Drug-Drug Interactions and Other Considerations With Direct-Acting Antivirals (DAAs)</td>
<td>Lucas A. Hill, PharmD&lt;br&gt;Ambulatory Care Pharmacist&lt;br&gt;University of California San Diego</td>
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<tr>
<td>1:25 – 1:35 PM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>1:35 – 2:05 PM</td>
<td>Hot Topics</td>
<td>Kenneth E. Sherman, MD, PhD</td>
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<td>2:05 – 2:15 PM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>2:15 – 3:15 PM</td>
<td>Future Areas of Debate Panel Discussion</td>
<td>Donald M. Jensen, MD</td>
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<tr>
<td>3:15 – 3:25 PM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>3:25 – 3:40 PM</td>
<td>Summary of Presentations and Closing Remarks</td>
<td>Donald M. Jensen, MD, and Kenneth E. Sherman, MD, PhD</td>
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Course Evaluation Notes

This form is included so that you may jot down any notes that you will use to complete the mandatory course evaluation, which will be e-mailed to you following the course.

<table>
<thead>
<tr>
<th>Presentations (content, presentation, objectives, lack of bias, etc)</th>
<th>Changes you intend to make in your clinical practice based on information presented</th>
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<tr>
<th>Parts of this activity that could have been improved</th>
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**Course Overview**

The program offers a dynamic course agenda that will focus on HCV infection. With the projected large increase in the number of patients who will require HCV treatment in the near future, clinicians who are experts in the complexities of antiretroviral management are uniquely well positioned to join our hepatology and gastroenterology colleagues in providing care for these patients, in what promises to be an exciting new era in HCV care.

Upon completion of the course, participants will be able to:

- Identify patients who should begin therapy
- Develop effective treatment regimens
- Describe the current data on available HCV protease inhibitor–based treatments, the emergence of resistance, and investigational and other direct-acting antivirals (DAAs) and interferon alfa regimens
- Describe the effects of HCV on the liver and be able to describe effective approaches for treating end-stage liver disease
- Describe drug–drug interactions, especially in HIV/HCV-coinfected patients on antiretroviral therapy
- Manage the adverse effects of HCV treatments

**EDUCATIONAL FORMAT**

In this course, information is presented through lectures and clinically relevant case studies developed by a distinguished faculty of expert HCV clinicians and researchers.

- **Lectures** provide state-of-the-art updates on timely and clinically relevant issues.
- **Case presentations** outline clinical scenarios, and attendees discuss their diagnostic or treatment choices. Faculty members use clinical decision points in case presentations as springboards for discussion of new data and current diagnostic and therapeutic issues in HCV management.

- **Question-and-Answer periods** give the audience, faculty, and panelists extended opportunities to review complex topics in HCV management.

We encourage you to provide your comments and suggestions on the online course evaluation form that you will receive following the course. We are especially interested in knowing how this course will contribute to measurable changes in your practice. In the months following this activity, we will ask you to complete a brief online survey, which will help facilitate this goal.

Please note that photographing, videotaping, or audio recording presentations is not permitted.

**ASSESSMENT OF NEEDS**

Rapid advances in treatment are anticipated with the introduction of DAAs to the HCV treatment paradigm. With the projected large increase in the number of patients who will require HCV treatment in the near future, clinicians who are experts in the complexities of antiretroviral management are uniquely well positioned to join our hepatology and gastroenterology colleagues in providing care for these patients, in what promises to be an exciting new era in HCV care.

**INTENDED AUDIENCE**

This course is designed for physicians and other health care practitioners who are experienced in the principles of complex chemotherapy (eg, antiretroviral therapy) and are actively treating or will be treating patients with HCV infection.

This activity is also relevant for other practitioners including nurse practitioners and other nursing professionals, physician assistants, pharmacists, and others.
Continuing Education Credits

CME CREDITS
Physicians (MD, DO, and international equivalents) are eligible to receive continuing medical education (CME) credit for their participation in this course. See the instructions below for claiming CME credits. Please keep this certificate for your records.

The International Antiviral Society–USA (IAS–USA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The IAS–USA designates this live activity for a maximum of 6.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CLAIMING CME CREDITS
CME-accredited providers are required to document the number of CME credits that each registered physician intends to claim for a CME activity. At the completion of the activity, a link to the evaluation form will be activated in your IAS–USA account under Registrations as well as sent via e-mail. Once you complete the evaluation, you will be directed to the online CME claim form, where you will note the actual number of hours that you participated in this CME activity.

To determine the CME credits that you can claim, count the time you spent attending presentations, panel discussions, and question-and-answer sessions. For example, if you attended 5 presentations at 30 minutes each, 4 question-and-answer sessions at 10 minutes each, and a panel discussion for 50 minutes, for a total of 4 hours, you would claim 4 CME credits. You may claim a maximum of 6.25 AMA PRA Category 1 Credits™ for this activity.

If the number of CME credits on your CME certificate is different from the number you noted as intending to claim, contact the IAS–USA to ensure that your records and our records match.
Continuing Education Credits

NURSING CONTINUING EDUCATION CONTACT HOURS

Education Review Systems is an approved approver of continuing nursing education by the Alabama State Nursing Association, an approved approver by the American Nurses Credentialing Center’s Commission on Accreditation. Provider # 5-115. This program is approved for 6 hours of continuing nursing education.

Educational Review Systems is also approved for nursing continuing education by the state of California, the state of Florida and the District of Columbia.

PHARMACY CONTINUING EDUCATION CONTACT HOURS

Educational Review Systems is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education. This program is approved for 6 hours (0.6 CEUs) of continuing pharmacy education credit. Proof of participation will be posted to your NABP CPE profile within 4 to 6 weeks to participants who have successfully completed the post-test. Participants must participate in the entire presentation and complete the course evaluation to receive continuing pharmacy education credit. ACPE # 0761-9999-14-271-L02-P

Other health care professionals will receive a certificate of participation.
POLICY ON DISCLOSURE AND CONFLICTS OF INTEREST

It is the policy of IAS–USA to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. All parties with control over the content of IAS–USA activities (eg, members of the Board of Directors, Advisory Board Members, activity chairs, authors, faculty, and IAS–USA staff) are required to disclose to the organization and activity audience any financial interest or other relationship with the manufacturer(s) of any commercial product(s) or provider(s) of commercial services with interests discussed in the activity (eg, presentation, article, etc) within the past 12 months. Financial interests or other relationships can include receipt of grants or research support, status as employee or consultant, stock or options holder, paid lecturer, paid writer/author, or member of speakers bureau, of the party or of his or her spouse or partner. The Accreditation Council for Continuing Medical Education (ACCME) defines a financial interest as an interest of any dollar amount.

It is IAS–USA policy to separate commercial promotion from its core educational and informational activities. Individuals who conduct marketing or promotional activities for commercial firms may not contribute to IAS–USA programs. A marketing or promotional activity includes any activity in which the commercial entity controls key elements, such as speaker or topic selection, that could be used to serve the entity’s commercial interests (eg, speakers bureaus, advertorials, etc). Individuals may not participate in most IAS–USA programs for 12 months after functioning in a promotional or marketing effort for a commercial firm. The Conference on Retroviruses and Opportunistic Infections, a research conference, does allow presenters to have such activities, but conflicts of interest are resolved before presenting.

IAS–USA policy requires that it resolve any real or apparent conflict of interest that may influence the development, content, or delivery of its educational activities prior to the activity being delivered to learners. The IAS–USA has several mechanisms for resolving conflicts of interest in educational activities. If the conflict of interest cannot be resolved through these mechanisms, the party will be removed from the activity. It is the policy of IAS–USA to publish the financial interests of all parties in control of the content of its activities on activity materials or, in cases where space is limited (eg, reprints of figures), on the IAS–USA website through a web address printed on the activity material. This information will also be provided directly by the IAS–USA office upon request.

The IAS–USA documents the date of the disclosure along with financial relationship information. As previously stated, the information published will reflect financial conflicts incurred within the previous 12 months. Individuals who refuse to disclose financial interests will not participate in the CME activity. It should be understood that other organizations may have different policies with regard to financial conflicts and with regard to the time period covered in the disclosure of financial conflicts.

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Bristol-Myers Squibb  
Gilead Sciences, Inc

**SILVER SUPPORTER**

Janssen Therapeutics

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**IAS–USA CME STAFF**

Donna M. Jacobsen, Executive Director, has no relevant financial affiliations to disclose.  
(Updated 10/8/14)

Cristin M. Toth, Director, CME Programs, has no relevant financial affiliations to disclose.  
(Updated 10/8/14)
Audience response touchpads are handheld, wireless terminals that enable the audience to respond anonymously to questions asked by the speaker. Attendees answer questions by pushing a button on the touchpad. Questions are multiple choice and the answers are tabulated immediately and displayed in a bar graph for the speaker and the audience to analyze.

Before and during the program, audience members are asked to answer a short series of demographic questions. These questions help determine the knowledge level and professional background of the audience and whether the audience response system is working properly. Please use the same touchpad throughout the day. Answers are linked only to the touchpad and not to the individual. Your participation is appreciated.

Participants are urged to choose answers based on their own experiences and preferences in treatment. Although some questions have definite right and wrong answers, many answers reflect current treatment trends, firsthand clinical or research experiences, and individual opinions. It is likely that the speaker will comment on the audience responses and, if appropriate, compare them with the approach chosen in the case under discussion. There is further discussion between the audience and the faculty in scheduled question-and-answer periods.

Keep these tips in mind when using the touchpads:

- Answers are anonymous and are not tracked to individuals in any way.
- Questions are multiple choice, and answers are numbered 1 to 10.
- You have approximately 5 to 10 seconds to enter an answer choice. A timer on the screen at the front of the room shows you how much time remains.
- Press your selection button firmly and only once.
- To cancel an answer and choose a new one, press another answer: this action deletes the first response. Answers may be changed only during the time allowed for each question.
- For demographic purposes, please note the number on the touchpad, and use the same touchpad throughout the day.
- If you think your touchpad is not working properly, please alert an IAS–USA staff member, who will try to provide you with another unit.

Please do not remove the touchpad from its plastic cover. Responses will transmit through the plastic.
Frequently Asked Questions and Common Abbreviations and Terms

How do I sign up for the IAS–USA mailing list and receive course announcements?

Log in to the IAS–USA website at www.iasusa.org. If you do not already have an account, please click on the “create new account” button located on our homepage.

Once you have created a username and password, you will be able to log in at any time to update and manage your online profile and to access up-to-date information on IAS–USA courses, publications, and activities.

How are topics and speakers selected?

The overall educational needs of the audience for any particular continuing medical education (CME) activity are determined by the participant evaluations from previous courses, results of epidemiologic research, perceptions of experts in the field, and recommendations of the IAS–USA Board of Directors and faculty. The Board of Directors and the course chairs are responsible for identifying and monitoring the needs of the target audience. The course chairs then design an agenda—choosing topics and inviting speakers—that meets the needs of the local audience. Our participants often suggest that particular topics be covered. The selection process prioritizes topics that meet the educational objectives of the majority of the participants.

Why don’t the slides in the course syllabus always match the presentation slides?

Faculty members are asked to submit their presentations to the IAS–USA 4 or 5 weeks before the course, to allow time for peer review and revision. Often, when faculty members review their slides at the faculty meeting—held the evening before the course—they make changes, to reduce overlap and to include the most up-to-date data.

Where and when do I receive a CME certificate?

At the completion of the activity, a link to the evaluation form will be activated in your IAS–USA account under Registrations as well as sent via e-mail. Once you complete the evaluation you will be directed to the online CME claim form, where you will note the actual number of hours that you participated in this CME activity. Your CME certificate will be available for you to print from your IAS–USA account immediately after you have submitted your claim form.

Can CME credits be awarded to nonphysicians?

American Medical Association (AMA) Physician’s Recognition Award CME guidelines state that only physicians are eligible to receive CME credits. Other health care professionals will receive a certificate of participation.

Can I request a reduced registration fee?

Although registration fees are low, the IAS–USA is flexible if a participant has an economic hardship. If you believe you qualify for a reduced registration fee, contact the IAS–USA prior to the course. Note that commercial companies may not pay the registration fees for health care practitioners to attend this course. Direct payment of registration fees by commercial companies is not permitted, as described in (among other documents) the AMA ethical position on gifts to physicians and the Accreditation Council for Continuing Medical Education (ACCME) guidelines.

How can I make a donation to the IAS–USA?

The IAS–USA is exempt from tax under section 501(c)(3) of the Internal Revenue Code. To make a tax-deductible donation to the organization, please see a staff member at the registration desk. Donation information is available on our website (www.iasusa.org). Donations are deposited in a specific fund for the distribution of Topics in Antiviral Medicine™ to HIV practitioners in developing countries.

How can I communicate my comments, questions, or suggestions about other IAS–USA programs?

We are very interested in what you have to say. For suggestions about this CME program, complete the online evaluation that you received at the start of the course. Or visit our website (www.iasusa.org/comments-and-suggestions), where you can share your comments with us. Send your comments, questions, or suggestions regarding other educational programs to info@iasusa.org.
Frequently Asked Questions and Common Abbreviations and Terms

Are IAS–USA live CME courses being recorded?
IAS–USA live CME courses are recorded for internet broadcast. By actively participating in a course and asking questions at the microphone, you agree to have your voice and comments used for the broadcast. If you would like to make a comment but do not wish to be recorded, please submit a question card to an IAS–USA staff member.

How do I order more drug resistance mutations cards or other resource cards?
To order resource cards, visit our online order form (www.iasusa.org/content/pocket-cards-order-form-0). You will need to log in or create an account on the IAS–USA website (www.iasusa.org).

Common Abbreviations and Terms
List of common abbreviations and terms is available on the IAS–USA website (www.iasusa.org/content/common-abbreviations-and-terms-hcv).

Check out our FAQ page at www.iasusa.org/frequently-asked-questions.
Learning Objectives

After attending this presentation, learners will be able to:

- Define the epidemiology and natural history of hepatitis C
- Determine the appropriate screening and confirmatory testing for hepatitis C
- Know the proper evaluation of a patient with known hepatitis C and considerations for treatment

Hepatitis C Virus

Basic Facts

- 27 nm single-stranded RNA virus: flaviviridae
- 3000 amino acid polyprotein
  - Structural: core and envelope
  - Nonstructural: protease, helicase, RNA-dependent RNA polymerase
- $10^{10}$-$10^{12}$ virions produced daily; turnover $\approx 3.5$ hrs
- Lack of proofreading ability can result in emergence of quasispecies
HCV Replication

1) Virus Entry
2) Uncoating
3) Protein Synthesis
4) Cleavage
5) RNA Replication
6) Packaging
7) Maturation
8) Re-infection

Hepatitis C Virus Genotypes in the USA

Type 1: 72%
Type 2: 17%
Type 3: 10%
All others: 1%


Hepatitis C Virus Infection Natural History

Acute HCV
- Resolved: 15% (15%)
- Chronic HCV: 85% (85%)

Chronic HCV
- Stable: 80% (68%)
- Cirrhosis: 20% (17%)
- Slowly progressive: 75% (13%)
- HCC: 25% (4%)

HCC, hepatocellular carcinoma
Histologic Progression of HCV

- Normal
- Mild Chronic Hepatitis
- Moderate Chronic Hepatitis
- Cirrhosis

Factors Associated With Disease Progression

- Alcohol consumption
  - 30 g/day in men
  - 20 g/day in women
- Disease acquisition at >40 years
- Male gender
- HIV coinfection
- Hepatitis B virus coinfection
- Immunosuppression


Future Burden of HCV-Related Morbidity and Mortality in the US

1 out of every 3 persons living with HCV infection today will die prematurely of HCV-related causes

Treatment-induced HCV clearance reduces annual patient care costs by half ($1436 to $717)
**HCV: A Major Cause of Liver Disease and Mortality**

- 36% of the 114,000 people on the liver transplant waiting list are HCV-infected\(^a\)
- 50% of all people with HCC are HCV-infected\(^b\)
- HCV-related liver disease is on the rise
  - 2-fold increase in HCV-related cirrhosis\(^c\)
  - 20-fold increase in HCC\(^d\)
  - 56% increase in HCV-associated mortality (1999-2007)\(^e\)

---

**Chronic HCV Infection: A Major Financial Burden in the United States**

Annual health-related work absence days for employees with and without HCV infection\(^a\):

- Annual sick leave: 2.65 vs 2.21
- Short-term disability: 4.17 vs 1.93
- Long-term disability: 1.36 vs 0.34

Healthcare-related costs among managed care enrollees with chronic HCV infection vs controls\(^b\):

- All-cause: $20,061 vs $5451
- Hospitalization (24% vs 7%)
- Mean inpatient costs ($5992 vs $1159)
- Prescriptions ($6191 vs $1315)

---

**Age-Adjusted Mortality Rates for HBV, HCV, and HIV**

*United States, 1999-2007*

![Graph showing age-adjusted mortality rates for HBV, HCV, and HIV from 1999 to 2007. The graph indicates that HCV-associated deaths occurred among people aged 45-64 years.*](image)

---

\(^c\) Anstee QM. *Gastroenterology* 2011;141:1195-1198.
The Public Health Challenge

How To Get People Into Care and Treatment
- Begins with identifying people who are infected
- The recommendations have been updated

Previous CDC Recommendations Based on Risk Factors and Medical Indications
- Past or present injection drug use
- Signs of liver disease (persistently elevated ALT)
- Received blood products made prior to 1987
- Received blood transfusion or organ donation prior to June 1992
- Past or present chronic hemodialysis
- Infants of HCV-infected mothers
- HIV infection

Recommendations for the Identification of Chronic HCV Infection Among People Born 1945-1965

In addition to testing adults at risk for HCV infection, the CDC recommends:
- Adults born during 1945-1965 should receive 1-time testing for HCV without prior ascertainment of HCV risk (strong recommendation, moderate quality of evidence), and
- All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions (strong recommendation, moderate quality of evidence)

Projected Health Impact of Birth Cohort Recommendations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Birth Cohort Testing With Therapy</th>
<th>PR</th>
<th>PR + DAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional cases identified</td>
<td>808,580</td>
<td>808,580</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis cases averted</td>
<td>138,000</td>
<td>203,000</td>
<td></td>
</tr>
<tr>
<td>Decompensated cirrhosis cases averted</td>
<td>50,000</td>
<td>74,000</td>
<td></td>
</tr>
<tr>
<td>HCC cases averted</td>
<td>32,000</td>
<td>47,000</td>
<td></td>
</tr>
<tr>
<td>Liver transplants averted</td>
<td>11,000</td>
<td>15,000</td>
<td></td>
</tr>
<tr>
<td>Deaths from HCV averted</td>
<td>82,000</td>
<td>121,000</td>
<td></td>
</tr>
<tr>
<td>Medical costs averted</td>
<td>$1.5 billion</td>
<td>$2.5 billion</td>
<td></td>
</tr>
<tr>
<td>Cost/QALY gained</td>
<td>$15,700</td>
<td>$35,700</td>
<td></td>
</tr>
</tbody>
</table>

DAA = direct-acting antiviral; PR = pegylated interferon and ribavirin.

References:
Comparison of HCV Cost Effectiveness With Other Routine Preventive Services

<table>
<thead>
<tr>
<th>Preventive Services</th>
<th>Cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer screening after age 50 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$11,000</td>
</tr>
<tr>
<td>HCV screening and treatment with pegylated interferon and ribavirin in birth cohort 1945-1965</td>
<td>$16,700</td>
</tr>
<tr>
<td>Influenza immunization after age 50 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$21,000</td>
</tr>
<tr>
<td>Hypertension screening and treatment after age 18 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$30,000</td>
</tr>
<tr>
<td>HCV screening and treatment with triple therapy in birth cohort 1945-1965</td>
<td>$35,700</td>
</tr>
<tr>
<td>HIV screening age 13-64 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$38,000</td>
</tr>
<tr>
<td>Cholesterol screening in high-risk people: men &lt;35 y, women &lt;45 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$38,000</td>
</tr>
<tr>
<td>Breast cancer screening after age 40 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$45,000</td>
</tr>
</tbody>
</table>


HCV Screening Test for Anti-HCV

Dects antibodies against HCV: evidence of host reaction

Hepatitis Confirmatory Tests for HCV RNA

Dects virus RNA: evidence of current infection
Nucleic Acid Tests

Use an FDA-approved test for HCV RNA

Qualitative test
- Determines if RNA is present or absent
- Anti-HCV+ and HCV RNA+ indicates active infection
  - Requires medical care
- Anti-HCV+ and HCV RNA- indicates past, resolved infection

Quantitative test
- Determines amount of RNA (viral load)
- Viral genotype

Benefits of Alcohol Intervention in HCV-Positive People

Alcohol is a cofactor for progression of liver disease

Clinician-directed intervention on alcohol use
- Mean reduction of drinking (g/wk) in the intervention groups was 38.42% lower than control group at ≥ 1 year follow-up

Your Patient Has HCV: What Do You Do Next?

History
- Risk factors
- Symptoms of disease

Physical examination
- Signs of advanced liver disease

Clinical evaluation
- Hepatitis activity grade
  - Determines rate of liver cell damage
- Fibrosis stage
  - Determines amount of liver cell damage
Who do you treat?

- Nearly all patients with chronic HCV are potential candidates given the safety and efficacy of newer therapies

**Monitoring the Untreated Patient**

**Blood tests**
- Liver biochemistry (e.g., ALT)
- Tests of synthetic function
- Platelet count

**Assessment of fibrosis**
- Repeat liver biopsy
- Noninvasive tests

**Surveillance for hepatocellular carcinoma in patients with cirrhosis**
- Liver ultrasound every 6 months
- AFP (optional)
Encourage Preventive Care

Avoid further liver damage
  - Abstinence from alcohol (maximum safe consumption is unknown)
  - Weight management
    - Prevent/reverse fatty liver
  - Coffee and tea consumption are beneficial in people with NAFLD

Encourage Preventive Care (cont)

Vaccines
  - Increased risk of severe acute viral hepatitis
    - HAV and HBV vaccines in people who are not immune

Herbal products
  - No known benefits, some are hepatotoxic
  - Silymarin (milk thistle) is the most commonly used herbal product in people with liver disease

Prescription medications
  - Weigh the risks and benefits of hepatotoxic medications

Encourage Safe Health Practices

Avoid sharing toothbrushes, other dental equipment, and shaving equipment

Cover bleeding wound(s)

Stop using illicit drugs; but, if not possible:
  - Avoid reusing or sharing syringes, needles, water, cotton balls or swabs, or other paraphernalia
  - Safely dispose of syringes and needles after 1 use

Do not donate blood, body organs, tissues, or semen

Always practice safe sex
And now, putting this all together with treatments today......
HCV is a LIVER Disease

Kenneth E. Sherman, MD, PhD
Gould Professor of Medicine
Director, Division of Digestive Diseases
University of Cincinnati Medical Center
Cincinnati, Ohio

ASSESSMENT OF HEPATIC FIBROSIS

Hepatic Fibrosis Is the Liver’s Wound-Healing Response to Many Chronic Injuries

- Hepatitis Viruses
- Inherited Metabolic Disorders
- Excess Vitamin A
- NASH
- Alcohol
- Drugs
- Immune Disorders
- Cholestatic Disorders

EDITED: 10-07-14
METHODS TO STAGE FIBROSIS

- Liver biopsy with histologic evaluation
  - Percutaneous
  - Aspiration
  - Cutting needle
  - Laparoscopic
  - Transjugular
- Elastography
  - Transient elastography/Acoustic Radiation Force Impulse (ARFI)
  - MRI
- Biomarkers (Serum)
  - Proprietary
  - Common tests

What Can Be Learned From a Biopsy?

- Severity of HCV
  - Degree of inflammation
  - Stage of Fibrosis
- Presence of other suspected findings (if you look)
  - Steatosis, NASH, ASH
  - Alpha-1 antitrypsin
- Presence of unsuspected findings
  - Granulomatous processes
  - Autoimmune diseases
  - Other

ARGUMENTS AGAINST LBX

- Adds few new data
- Difficult, time consuming and dangerous
- Not reproducible- Not a GOLD standard
- Costly
- “Patient’s don’t want a biopsy”
- Not needed with current therapies
### Fibrosis Stages in Hepatitis

<table>
<thead>
<tr>
<th>Ishak</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metavir</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Batts-Lu</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

### Fibrosis/Cirrhosis

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How Accurate is the Biopsy

- Will never overstage disease - 50% less variation than non-invasive tests
- Highly reliable if done correctly
  - Persico et al. AM J GASTRO 2002 - Minimal variation between paired biopsies of left and right lobes when bx >25 mm
- High concordance between/within review of trained pathologists

Pathologic Staging of Fibrosis

Size vs Accuracy – 161 Patients

<table>
<thead>
<tr>
<th>Bx Length</th>
<th>Cirrhosis*</th>
<th>No Cirrhosis</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 cm</td>
<td>7.4%</td>
<td>92.6%</td>
<td>1.00</td>
<td>0.96</td>
<td>96%</td>
</tr>
<tr>
<td>1.0 cm</td>
<td>4.9%</td>
<td>95.1%</td>
<td>1.00</td>
<td>0.93</td>
<td>94%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bx Length</th>
<th>Signif Fibr**</th>
<th>No Signif Fibr</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 cm</td>
<td>41.0%</td>
<td>59.0%</td>
<td>1.00</td>
<td>1.00</td>
<td>100%</td>
</tr>
<tr>
<td>1.5 cm</td>
<td>31.6%</td>
<td>66.4%</td>
<td>1.00</td>
<td>0.86</td>
<td>91%</td>
</tr>
<tr>
<td>1.0 cm</td>
<td>19.8%</td>
<td>80.2%</td>
<td>1.00</td>
<td>0.74</td>
<td>78%</td>
</tr>
</tbody>
</table>

Colloredo et al, J Hepatol 2003

IMPACT OF NUMBER OF PORTAL AREAS

Colloredo et al, J HEPATOL 2003
TRANSIENT ELASTOGRAPHY

- Measures elasticity using sound waves
- Stiffness determined by multiple factors
  - Degree of fibrosis
  - Degree of inflammation
  - Cannot be used in acute hepatitis
  - Degree of steatosis
  - Iron accumulation
- Approved in U.S. 2013
  - XL special probe for obese patients
  - Very expensive to purchase unit: $131K


Transient Elastography
Meta-analysis

- Meta-analysis of 50 studies assessed the overall performance of transient elastography for diagnosing liver fibrosis.
- The areas under the receiver operating characteristic curve were:
  - For significant fibrosis: 0.84 (95% CI 0.82–0.86)
  - For severe fibrosis: 0.89 (95% CI 0.88–0.91)
  - For cirrhosis: 0.94 (95% CI 0.93–0.95)
- Failure rate: 2.4–9.4% (Castera et al., 2008, J HEPATOLOGY)

Friedrich-Rust et al Gastroenterology 2008; 134:960–974

ARFI (Acoustic Radiation Force Impulse)

Takahashi et al., LIVER INT 2009
**Elastography and portal hypertension**

![Graph showing linear regression analysis between HVPG and LSM in whole patient population.](image1)

**Transient Elastography**

Liver Stiffness vs. Outcomes

De Ledinghen et al, GASTROENTEROL CLIN BIO, 2008

**MRI Elastography**

- Similar to transient elastography but can demonstrate the liver stiffness in the whole organ, and is color coded
- Can distinguish Child-Pugh grade A cirrhosis from other grades to be 93% sensitive and 82% specific

Ito et al AJR Am J Roentgenol 1999; 173:591–596
Slide 29 of 55

**FIBROTIC PROGRESSION**

- Mild
- Moderate
- Severe fibrosis
- Cirrhosis - mild
- Cirrhosis - severe
- HCC

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
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</thead>
<tbody>
<tr>
<td>%</td>
<td>0-33%</td>
<td>0-33%</td>
<td>0-33%</td>
<td>0-33%</td>
<td>0-33%</td>
<td>0-33%</td>
</tr>
</tbody>
</table>

adapted from Afdhal, Sem Liver Disease, 2004

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Slide 30 of 55

**Rapid Progression of Liver Disease in HIV/HCV-Coinfected Patients**

- Prospective study of fibrosis progression in 67 coinfected patients
- 2 biopsies; median time between biopsies was 2.84 years

- Change in Ishak Score From First to Second Biopsy
  - >25% of patients with mild fibrosis on initial biopsy had ≥2 stage progression in fibrosis score
  - Patients With Mild Fibrosis (≤F1) on First Biopsy

---

Slide 31 of 55

**HCV in Cirrhotic Patients**

- Risk of Decompensation and HCC

- Fattovich et al., Gastroenterology 1997; 112:463
HEPATIC DECOMPENSATION

- Ascites
  - Hepato-renal syndrome (HRS)
  - Hepatic hydrothorax
  - SBP
- Encephalopathy
- Bleeding varices
- Coagulopathy (PT >3 seconds>control)

Clinical Staging of Cirrhosis: Child-Turcotte-Pugh Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Bilirubin (mg/dL)</th>
<th>Albumin (g/dL)</th>
<th>PT (INR)</th>
<th>Hepatic Encephalopathy</th>
<th>Ascites (grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;2</td>
<td>&gt;3.5</td>
<td>&lt;1.7</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>2–3</td>
<td>2.8–3.5</td>
<td>1.8–2.3</td>
<td>1–2</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>&gt;3</td>
<td>&lt;2.8</td>
<td>&gt;2.3</td>
<td>3–4</td>
<td>Severe</td>
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</tbody>
</table>

Child Class

- A 5–6
- B 7–9
- C >9


MELD

- Model For End-Stage Liver Disease
  - Bilirubin
  - Creatinine
  - INR
- Used to predict mortality and time for OTL Tx
  - Example: Creatinine 1.6; Bili 1.4; INR 1.6
  - MELD=17
  - Estimated 3-month mortality: 18%
SPLANCHNIC CIRCULATION

ASCITES

COMPLICATIONS OF ASCITES
• Pain/Discomfort
• SBP
• Hepatic Hydrothorax
• HRS
WHEN TO TAP ASCITES

- First time ascites discovered
- Every time patient is admitted to hospital
- With all changes in status

HOW TO TAP ASCITES

- Diagnostic
  - Subumbilical with 1" needle on syringe
  - Patient sitting at 30-degree angle
  - DO NOT NEED INTERVENTIONAL RADIOLOGY, PLATELETS, OR FFP
  - Obtain
    - Cell count
    - Culture directly into bottles at bedside
- Therapeutic
  - Caldwell needle
  - Replace albumin if creatinine increased or >5 L (12 grams/liter removed)
Management of Ascites

First-Line Therapy

- Tense ascites
  - Paracentesis
  - Sodium restriction (<2 gm/24 hrs) and diuretics
  - Non-tense ascites

Second-Line Therapy

- Refractory ascites 10%
  - Repeated large-volume paracentesis (LVP)
  - TIPSS
  - Liver transplantation

Diuretics: Spironolactone 50 mg/day, furosemide 20 mg/day or bumetanide 1 mg a day

*Titrate response to spironolactone 400 mg/day, furosemide 160 mg/day or bumetanide 4 mg/day as long as it is tolerated AT 2-WEEK INTERVALS

HEPATIC HYDROTHORAX

- CHEST TUBE

VARICES
Cirrhosis

Prevalence 35%-80%

Risk of Bleeding: Esophageal Varices

25%-40%

Die

30%-50% 50%-70%

Survive

Rebleed

70%

Risk of Bleeding

VARICEAL SURVEILLANCE

EGD

No varices

Repeat endoscopy in 3 years (well compensated); in 1 year if decompensated

No beta-blocker prophylaxis

Small varices (<5 mm), child B/C

Non-selective beta-blocker prophylaxis

Medium or large varices

Child Class A, no red wales-beta blockers

Child class B/C, red wales-beta blockers, or band ligation

HEPATIC ENCEPHALOPATHY

[Image of hand with cirrus sign]
ETIOLOGY AND PROGNOSIS

• Shunting of gut-derived neuroactive substances (mostly nitrogen based) that cross blood-brain barrier and act as inhibitory neurotransmitters
  – Survival probability
    • 42% at 1 year
    • 23% at 3 years

HE

Precipitating Factors

• High-protein meal
• GI bleed
• Infection (SBP)
• Vascular thrombosis
• HCC
• Poor compliance with HE treatment

TREATMENT

• Lactulose
• Neomycin
• Metronidazole
• Rifaximin
Rifaximin Treatment in HE: Time to First Breakthrough HE Episode (Primary End Point)

Proportion of Patients Without Breakthrough HE (%)

- Rifaximin*: 77.9%
- Placebo*: 54.1%

Hazard ratio with rifaximin, 0.42 (95% CI, 0.28–0.64)
P<0.001

Days Since Randomization


MHE: Associated With Motor Vehicle Crashes
Predictive Accuracy of Diagnostic Testing

Percentage of patients with crashes by SELF-REPORT according to MHE status and diagnostic test (n=120)

- Positive
- Negative

P=0.004

Percentage of patients with crashes by DOT according to MHE status and diagnostic test (n=167)

- Positive
- Negative

P=0.004


HCC SURVEILLANCE

- Ultrasound
  - Every 6 months
  - Subjective, experience matters
- AFP and related markers
  - Not recommended by AASLD
  - Used by most hepatologists
LIVER TRANSPLANTATION

When to Refer

• Any hepatic decompensation
  – Ascites
  – Encephalopathy
  – Variceal bleeding
• MELD >10
• HCC

SUMMARY

• HCV is ALSO a liver disease
  – Ask whether advanced fibrosis is present
  – If yes, start surveillance for
    • Varices (EGD)
    • Ascites (US)
    • HCC (US)
• CONTACT HEPATOLOGIST EARLY WHEN ANY SIGN OF DECOMPENSATION IS PRESENT
• MANAGE THE COMPLICATIONS!!
Learning Objectives

After attending this presentation, learners will be able to:

- Assess the different therapeutic options for hepatitis C genotypes 1-6, both treatment naïve and treatment experienced
- Assess the treatment options for hepatitis C and liver transplantation
- Know the similarities in treatment outcomes between HCV monoinfection and HCV/HIV coinfection

Pre-Treatment Evaluation Should Include:

- Evaluate for limitations to therapy
  - There are few absolute contraindications to HCV therapy
- Education regarding transmission, prognosis
- Smoking and alcohol cessation counseling
- Assess degree of fibrosis
- HBV and HAV vaccination
- HIV, HBV testing
**Benefit of SVR**

1. Improves histology
2. Decreases risk of cirrhosis, liver cancer and transplantation
3. Improves quality of life
4. Improves insulin resistance
5. Decreases all-cause mortality

**Multiple Classes of Direct-Acting Antiviral Agents**

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<tr>
<th>Target</th>
<th>NS5A inhibitors</th>
<th>NS5B Non-NUC inhibitors</th>
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**Resistance Variants by Class**

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Current Standard of Care: Genotype-1

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<tr>
<td>Alt*</td>
<td>SMV + PEG + RBV</td>
<td>PEG + RBV</td>
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</tbody>
</table>

*If genotype 1a, check baseline Q80K mutation prior to initiating treatment.
| Interferon ineligible: | | | | |
| Rec | Alt | Alt* | Alt* | PEG + RBV |

If failed prior therapy with telaprevir or boceprevir.

What’s the evidence?
Genotype 1

Sofosbuvir + PEG + RBV: NEUTRINO Phase 3 Study Design

- Open label
  - Sofosbuvir 400 mg QD + PegIFN-2a 180 µg/week + RBV 1000-1200 mg/day for 12 weeks (no response-guided therapy)
- Treatment-naive, genotype 1, 4, 5, and 6, HCV-infected patients
  - 89% of patients had genotype 1 HCV
  - 17% of patients had cirrhosis

Simeprevir + PEG/RBV in GT1, Tx-Naive Patients: 
**QUEST-1/2 Phase 3 Trial Design**

- **Response-Guided Treatment**
- **N=521**
  - SMV 150 mg OD + PR
  - Placebo + PR

- **N=264**
  - Weeks 0 12 24 48 72

  - **RGT in simeprevir arm:** If HCV RNA < 25 IU/mL at Wk 4 and undetectable at Wk 12, complete treatment at Wk 24; otherwise, continue treatment to Wk 48
  - **Stopping rules:**
    - If HCV RNA > 1000 IU/mL at Wk 4, stop SMV/placebo
    - If HCV RNA < 2 log10 IU/mL reduction at Wk 12, or confirmed > 25 IU/mL at Wk 24 or 36, stop all treatment

  - 

**Additional Notes**


---

**Simeprevir + PEG/RBV: Phase 3 QUEST-1:** 
Impact of Subtype & Fibrosis Stage in GT 1

- **SVR (%):**
  - GT 1b > GT 1a
  - F0-F2 > F4


---

**Simeprevir + PEG/RBV: Phase 3 QUEST-1:** 
Impact of Subtype & Q80K

- **SMV + P/R vs Placebo + P/R**

COsmos: Simeprevir + Sofosbuvir ± RBV in Genotype 1 HCV: Phase 2a Study Design

- Cohort 1: Prior null responders (METAVIR F0-F2)
- Cohort 2: Treatment-naive and prior null responders (METAVIR F3-F4)
- SMV 150 mg QD + SOF 400 mg QD +/- RBV 1000/1200 mg/day

QD, once daily; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; SVR4, sustained virologic response 4 weeks after planned treatment end; SVR12, sustained virologic response 12 weeks after planned treatment end.

Off-label Combination of Sofosbuvir (NUC) and Simeprevir (PI): COsmos

- Relapse in 3 pts in Cohort 1, and 3 pts in Cohort 2.
- SVR in Q80K+ = 86%-100%

COSMOS: Cohort 1
F0-F2; Prior Nulls

- Relapse in 3 pts in Cohort 1
- SVR in Q80K+ = 86%-100%

Excludes non-virologic failures

SMV + SOF + RBV
SMV + SOF

Overall

- 1a
- Q80K+
- 1a
- Q80K-

96
93
93
93
96
93
93
96
93
93
93
93

COSMOS: Cohort 2
F3-F4; Naives and Nulls

- Relapse in 3 pts in Cohort 2.
- SVR in Q80K+ = 86%-100%

Genotypes 2-6

Current Standard of Care: Genotypes 2-6
Current Standard of Care: Treatment-Experienced Genotypes 2-6

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<th>Genotype</th>
<th>Treatment Experienced</th>
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<td>Geno-3</td>
<td>Rec SOF + RBV</td>
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www.HCVguidelines.org

What's the evidence?

Genotype 2

Genotype 2
Treatment-naive patients with GT 2/3 HCV (N = 499)
Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day (n = 70)
PegIFN + RBV 800 mg/day (n = 67)
Wk 12 Wk 24
SVR12
No cirrhosis Cirrhosis
98% 82%
91% 62%

FISSION

Treatment-naive patients with GT 2/3 HCV (N = 400)

FUSION

Treatment-experienced patients with GT 2/3 HCV

Gane E, et al. EASL 2013. Abstract S.
Pts with HCV GT2 or GT3 and previous treatment failure with P/R (N = 47)

Sofosbuvir 400 mg QD + PegIFN wkly + RBV 1000 mg or 1200 mg

Wk 12

SVR12

All GT-2  F2, GT-2  F4, GT-2

96%  100%  93%

LONESTAR-2

No cirrhosis  Cirrhosis

POSITRON

No cirrhosis  Cirrhosis

No interferon, intolerant, or ineligible pts with GT 2/3 HCV (N = 278)

Sofosbuvir 400 mg GT - RBV 1000-1200 mg/day (N = 109)

Placebo (N = 71)

SVR12

IFN unwilling, intolerant, or ineligible pts with GT 2/3 HCV (N = 278)

Sofosbuvir 400 mg QD + PegIFN daily + RBV 1000 mg or 1200 mg

Wk 12

SVR12

All GT-2  F0-3, GT-2  F4, GT-2

96%  100%  93%

What’s the evidence?

Genotype 3

Treatment-naive patients with GT 2/3 HCV (N = 499)

Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day (n = 183)

PegIFN + RBV 800 mg/day (n = 176)

Wk 12

SVR12

No cirrhosis  Cirrhosis

FUSION

Treatment-experienced patients with GT 2/3 HCV

SOF + RBV (n = 32)

Wk 12

SVR12

No cirrhosis  Cirrhosis

FISSION

Treatment-naive patients with GT 2/3 HCV (N = 499)

Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day (n = 183)

PegIFN + RBV 800 mg/day (n = 176)

Wk 12

SVR12

No cirrhosis  Cirrhosis

FUSION

Treatment-experienced patients with GT 2/3 HCV

SOF + RBV (n = 32)

Wk 12

SVR12

No cirrhosis  Cirrhosis

FUSION

Pts with HCV GT2 or GT3 and previous treatment failure with P/R (N = 48)

SOF + PEG + RBV (n = 48)

Wk 12

All GT

-3 F4, GT -3 F0 -3, GT -3 83%

Wk 12 Wk 24

95% 92%

No cirrhosis Cirrhosis

Genotype 3

Impact of Duration on Efficacy of SOF in Treatment-Experienced GT 3

FUSION: 12 Wks SOF/RBV
FUSION: 16 Wks SOF/RBV
VALENCE: 24 Wks SOF/RBV

SOF, sofosbuvir; RBV, ribavirin.

Retreatment in GT 3 Pts With Previous SOF + RBV Failure

Open-label, nonrandomized trial
34% to 41% compensated cirrhosis

12 weeks SOF+PEG/RBV 24 weeks SOF/RBV

SOF/RV12 (%)
Liver Transplantation

Phase 2 Pre–Liver Transplant Pilot Study
SOF + RBV to Prevent HCV Recurrence Post Transplant

- Inclusion criteria:
  - Meeting MILAN criteria undergoing LT for HCC 2° to HCV
  - Model for End-Stage Liver Disease (MELD) ≤ 22 and HCC-exception MELD ≥ 22
  - Compensated cirrhosis: Child-Pugh-Turcotte score ≤ 7

VIRAL RESPONSE

Liver transplant (up to 46 weeks)

SOF 400 mg + RBV 1000-1200 mg

At OLT

Post-Wk12

93%

69%


Analysis of Post-Transplant Recurrence in GT 1-4
Days HCV RNA Continuously TND Prior to Transplant

No recurrence (n=28) Recurrence (n=10)*

Median days TND

- No recurrence: 95
- Recurrence: 5.5
p <0.001

*3 patients with recurrent HCV had 0 consecutive days TND before transplant.

Phase 2 Post–Liver Transplant Study Design
SOF + RBV for Established Recurrent HCV Post Liver Transplant

- Primary endpoint: SVR12 in patients with recurrent HCV post LT
- Study inclusion criteria:
  - Liver transplant ≥ 6 months and ≤ 150 months
  - CPT ≤ 7 and MELD ≤ 17
  - Exclusion: Prednisone > 5 mg/day
- No episodes of acute or chronic rejection
- No interactions between immunosuppressants and SOF
  - 4 patients increased tacrolimus dosing due to improved liver function


HIV/HCV Sofosbuvir Study

Similar response rates in HCV/HIV–co-infected patients compared to HCV–mono-infected patients

Summary

- Currently approved and recommended therapy for HCV represents a marked improvement over prior treatments by having:
  - Higher SVR rates
  - Improved tolerability
  - Shorter treatment duration
  - Easier monitoring
Future Therapies for HCV: What Is Coming in the Next 6 Months?

Andrew Aronsohn, MD

Assistant Professor of Medicine
University of Chicago Medical Center
Chicago, Illinois

**Learning Objectives**

After attending this presentation, learners will be able to:

- Identify upcoming therapies for treatment-naive patients
- Understand upcoming therapies for treatment-experienced patients
- Formulate plan of treatment decision making based in new therapies

---

**Case #1**

WM is 57 years old with genotype 1b HCV. He is naïve to therapy. He had a liver biopsy in 2008 when he was diagnosed, which revealed stage 2 disease. He currently feels well with no complaints. Physical exam is unremarkable. Labs reveal: Normal LFTs except AST 83 U/L (normal 8-37) and ALT 68 U/L (normal 8-35). HCV viral load: 288673 IU/mL. Platelets 143K. Ultrasound is unremarkable. WM is interested in newer therapies.
New Therapy Overview

- Mostly for Genotype 1
- Will include treatment-naive, treatment-experienced, cirrhosis
- All oral
- Combinations of different mechanisms of action
- Almost all 12 weeks
- Minimal side effects
- Anticipated 1-6 months

Structure of HCV Genome: Protease Inhibitors

Nucleoside/tide Polymerase Inhibitors Mechanism of Action
HCV NS5a Replication Complex: Another Therapeutic Target

Structure of NS5A domain associated with endoplasmic reticulum (ER)

- Large phosphoprotein
- Associates at least as a dimer
- Binds RNA
- Amphipathic helix (H) at amino terminus promotes membrane association
- Essential component of HCV RNA ER-membrane-associated replication complex
- Modulates cellular systems involved in IFN resistance


The Next Generation of DAAs

<table>
<thead>
<tr>
<th>DAA Class</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>ABT-450/r Ombitasvir</th>
<th>Daclatasvir</th>
<th>Asunaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease Inhibitor</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS5A Inhibitor</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleoside Polymerase Inhibitor</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Nucleoside Polymerase Inhibitor</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Slide courtesy of Donald Jensen MD

Anticipated Treatment Options

<table>
<thead>
<tr>
<th>Study</th>
<th>Wks</th>
<th>SVR Geno-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF + LDV</td>
<td>12-24</td>
<td>97-99%</td>
</tr>
<tr>
<td>ABT450/r+OBV+DSB+RBV</td>
<td>12</td>
<td>97-99%</td>
</tr>
<tr>
<td>DCV+ASV (geno-1b)</td>
<td>24</td>
<td>84-90%</td>
</tr>
<tr>
<td>Treatment-Experienced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF + LDV</td>
<td>12-24</td>
<td>94-99%</td>
</tr>
<tr>
<td>ABT450/r+OBV+DSB+RBV</td>
<td>12</td>
<td>96%</td>
</tr>
<tr>
<td>ABT450/r+OBV+DSB+RBV</td>
<td>12-24</td>
<td>98-100%</td>
</tr>
<tr>
<td>DCV + ASV (geno-1b)</td>
<td>24</td>
<td>82%</td>
</tr>
</tbody>
</table>

Slide courtesy of Donald Jensen MD
Treatment Naive
Genotype 1

ION 1: Ledipasvir + Sofosbuvir in Treatment-Naive Patients

- LDV = NSSA inhibitor
- SOF = Polymerase inhibitor
- +/- Ribavirin
- 12 or 24 weeks
- Well tolerated
- Genotype 1
- 97-99% SVR

Afdhal et al NEJM 2014

Sofosbuvir + Ledipasvir: Duration of Therapy

SVR 12 %

Kowdley et al NEJM 2014
Sofosbuvir + Ledipasvir

Duration of Therapy

Kowdley et al. NEJM 2014

Sofosbuvir + Ledipasvir
Duration of Therapy

Kowdley et al. NEJM 2014

Sofosbuvir / Ledipasvir

http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf

Sofosbuvir + Daclatasvir

• DCV = NSSA inhibitor
• SOF = polymerase inhibitor
• +/- ribavirin
• Study included
  – Tx naive
  – Tx experienced
  – G 1,2,3
  – 12-24 weeks

Previously Untreated G1 Patients

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/DCV</td>
<td>24 wk</td>
<td>100%</td>
</tr>
<tr>
<td>SOF/DCV/RBV</td>
<td>24 wk</td>
<td>100%</td>
</tr>
<tr>
<td>SOF/DCV</td>
<td>12 wk</td>
<td>93%</td>
</tr>
<tr>
<td>SOF/DCV/RBV</td>
<td>12 wk</td>
<td>93%</td>
</tr>
</tbody>
</table>

Sulkowski et al. NEJM 2014

Sulpizio et al. NEJM 2014

http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf
ABT 450/r + Ombitasvir + Dasabuvir

- ABT 450 = protease inhibitor (boosted with ritonavir)
- Ombitasvir = NS5A inhibitor
- Dasabuvir = non-nucleoside polymerase inhibitor
- + Ribavirin

Feld et al NEJM 2014

Daclatasvir and Asunaprevir

- Daclatasvir = NS5A
- Asunaprevir = protease inhibitor
- Genotype 1b only
- 135 Treatment-naive

Genotype 1 Treatment Experienced
Case #2

WM is 57 years old with genotype 1b HCV. He was previously treated in 2008 with PEG/RBV and was a null responder. His liver biopsy showed stage 2 disease. He currently feels well with no complaints. Physical exam is unremarkable. Labs reveal: Normal LFTs except AST 83 U/L (normal 8-37) and ALT 68 U/L (normal 8-35). HCV viral load: 288673 IU/mL. Platelets 143K. Ultrasound is unremarkable. WM is interested in newer therapies.

Retreatment With Upcoming Agents

- All IFN free
- May or may not require RBV
- Response rates are similar for many as treatment naive
- Most studies included previous null responders
- Duration at least 12 weeks

Expected therapy for G1 treatment experienced patients (PEG/RBV)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>N</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV + SOF +/- RBV</td>
<td>12 - 24 wks</td>
<td>440</td>
<td>94 - 99%</td>
</tr>
<tr>
<td>SOF + DCV +/- RBV</td>
<td>12 - 24 wks</td>
<td>41</td>
<td>95 - 100%</td>
</tr>
<tr>
<td>ABT450/r + Ombitasvir + Dasabuvir + RBV</td>
<td>12 - 24</td>
<td>222</td>
<td>87 - 100%</td>
</tr>
<tr>
<td>DCV + ASV</td>
<td>12</td>
<td>205</td>
<td>82% (all G1b)</td>
</tr>
</tbody>
</table>

Poordad et al NEJM 2014
Afdhal et al NEJM 2014
Sulkowski et al NEJM 2014
Manns et al Lancet 2014
Case #3

WM is 57 years old with genotype 1b HCV. He was previously treated in 2011 with PEG/RBV/Telaprevir and discontinued therapy at week 6 due to adverse events (severe rash). He currently feels well with no complaints. Physical exam is unremarkable. Labs reveal: Normal LFTs except AST 83 U/L (normal 8-37) and ALT 68 U/L (normal 8-35). HCV viral load: 288673 IU/mL. Platelets 143K. Ultrasound is unremarkable. WM is interested in newer therapies.

New Agents for PI Nonresponse (avoid retreatment with PI)

Polymerase inhibitor (sofosbuvir) +
NS5A inhibitor (ledipasvir or dacatasvir)

New Agents: PI Failures
SOF + LDV +/- RBV

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Prev Tx: TVR (n)</th>
<th>Prev Tx: Boc (n)</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV + SOF</td>
<td>43</td>
<td>39</td>
<td>94%</td>
</tr>
<tr>
<td>LDV + SOF + RBV</td>
<td>16</td>
<td>19</td>
<td>96%</td>
</tr>
</tbody>
</table>

Afshal et al 2014
New Agents: PI Failures
SOF + DCV

- 41 patients previously treated with protease inhibitors
- 40/41 (98%) with SVR

Sulkowski et al 2014

Case #4

- AP is 53 yo with G1 HCV. Previous non-responder to PEG/RBV therapy 8 years ago. She was diagnosed with cirrhosis by imaging (CT scan). Her course has been complicated by trace ascites which is well controlled on low-dose diuretics. She has no history of varices or hepatic encephalopathy. Her MELD score is 8. She comes to clinic to inquire about HCV therapy.

SVR and Decompensation and HCC in Cirrhotic Patients

Fernandez-Rodriguez et al 2010
SVR and Survival in Patients with Cirrhosis

Fernandez-Rodriguez et al 2010

AASLD/IDSA/IAS–USA Guidance

Upcoming Treatment Options in Cirrhotic Patients
SVR rates are similar, but vary more in cirrhotics

<table>
<thead>
<tr>
<th>Study</th>
<th>Wks</th>
<th>Geno-1 cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF + LDV</td>
<td>12 - 24</td>
<td>97 - 100%</td>
</tr>
<tr>
<td>ABT450/r + OBV + DSB + RBV</td>
<td>12 - 24</td>
<td>94%</td>
</tr>
<tr>
<td>DCV + ASV (geno-1b)</td>
<td>24</td>
<td>84%*</td>
</tr>
</tbody>
</table>

Treatment-Experienced

<table>
<thead>
<tr>
<th>Study</th>
<th>Wks</th>
<th>Geno-1 cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + LDV</td>
<td>12 - 24</td>
<td>82 - 100%</td>
</tr>
<tr>
<td>ABT450/r + OBV + DSB + RBV</td>
<td>12 - 24</td>
<td>86 - 100%</td>
</tr>
<tr>
<td>DCV + ASV (geno-1b)</td>
<td>24</td>
<td>84%*</td>
</tr>
</tbody>
</table>

Slide courtesy of Donald Jensen MD
Sofosbuvir/ Ledipasvir

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommended Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive with or without cirrhosis</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment-experienced with cirrhosis</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Treatment-experienced without cirrhosis</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

* HAP*POI for 4 weeks can be considered in treatment-naive patients with cirrhosis who have pre-treatment HCV RNA less than 8 million IU/mL. [See Clinical Studies / 147]
** Treatment-experienced patients who have failed treatment with other peginterferon alfa + ribavirin or an HCV protease inhibitor + peginterferon alfa + ribavirin.

[Sulkowski et al NEJM 2014](http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf)

Genotype 2 and 3

New Therapy In G2 and G3*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>n</th>
<th>SVR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/DCV</td>
<td>24 week</td>
<td>30</td>
<td>93%</td>
</tr>
<tr>
<td>SOF/DCV/RBV</td>
<td>24 week</td>
<td>14</td>
<td>93%</td>
</tr>
</tbody>
</table>

*All Treatment Naive

[Sulkowski et al NEJM 2014](http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf)
Summary

• New options for almost ALL genotype 1 HCV patients
  – Data still lacking for: CKD, decompensated cirrhosis
• Combinations of 2-3 drugs with unique mechanisms
• All will be great in HCV, except...

Cost

Access
Strategies for Treating HCV Infection in HCV/HIV-Coinfected Patients

David L. Wyles, MD
Associate Professor of Medicine
University of California San Diego
La Jolla, California

Learning Objectives
After attending this presentation, learners will be able to:

- Understand the available data on the use of novel DAA regimens to treat HCV in those with HIV-1
- Recognize pertinent drug interaction between HCV treatment regimens and antiretrovirals
- Develop a framework for treating HCV in those with HIV with new DAA regimens

WHEN AND IN WHOM TO INITIATE THERAPY

High Priority for Treatment Owing to High Risk for Complications

- Fibrosis (Metavir F2)
  - Rating: Class I, Level B
- HIV-1 coinfection
  - Rating: Class I, Level B
Potential Issues in Treating HIV/HCV Co-infection With New HCV Antivirals

Efficacy
DDI
HCV Therapy in HCV/HIV
Access
Providers

EFFICACY OF DAA THERAPIES IN CO-INFECTION

Peg/RBV plus DAA in HCV/HIV
Results indicate similar efficacy in co-infected subjects

PHOTON: SOF/RBV FOR HIV/HCV

Cirrhosis permitted
Most ART allowed
- CD4>500 not on ART
- CD4>200 on ART

SOF/RBV (n=114)
SOF/RBV (n=68)
SOF/RBV (n=41)

GT1 TN
GT2,3 TN
GT2,3 TE

SOF/RBV (n=19)
SOF/RBV (n=55)
SOF/RBV (n=200)

GT2 TN
GT1,3,4 TN
GT2 TE

PHOTON 2: 65% (11/17) GT1 cirrhosis; 78% (18/23) GT 3 TE, cirrhosis

SOF/LDV in those with HIV

FDC: SOF 400mg/LDV 90mg PO QD
- Group 1: no ART
  - CD4>500 or HIV <500 with “stable” CD4
- Group 2: CD4>100 and HIV <40
  - Allowed: EFV, RAL, or RPV

Group 1
Group 2

Male 54% 81%
African American 77% 86%
1a 75% 81%
F3 38% 22%
CD4 687 576
SOF/LDV in those with HIV

- One HIV BT due to non-compliance, re-suppressed
- Grade 3/4 AEs: neutropenia (1), AST (1), CPK (1)
- Ongoing phase 3 study: ION-4

TURQUOISE I: 3D + RBV in HIV/HCV

- Stable ART
  - ATV or RAL (part A)
  - HIV RNA <40 copies/mL
  - CD4 >200

- 2 Virologic failures
  - Both 1a cirrhotic null responders
  - Relapse in 12-wk arm
  - BT at week 16
- Well tolerated
  - No discontinuation due to AEs
  - 5 HIV VL ≥40 copies/mL
  - None ≥200 copies/mL
  - All re-suppressed
- DRV arms added (part B)
- Phase 3 portion following

Full SVR12 data to be presented at AASLD. Wyles DL. #1939 AASLD 2014.
The COSMOS regimen in co-infection: What are the issues?

• No clinical trial data in co-infection
  – Pilot study planned (NCT02206932)
  – Efficacy probably not a concern
• Simeprevir: significant DDI potential
  – CYP3A4 substrate (hepatic)
  – CYP3A4 inhibitor (intestinal)
• Sofosbuvir: low DDI potential
  – Not a CYP3A4 substrate/inhibitor
  – P-gp and BCRP substrate
  – Modest increase in TFV Cmax

DRUG-DRUG INTERACTIONS WITH ANTIRETROVIRALS

Simeprevir drug interactions

• No significant interaction: TDF, RAL, RPV (DTG)
• Significant interaction with PI/rit, EFV

Ouwerkerk-Mahadevan S. IDSA 2012.

EFV DRV/rit
Sofosbuvir and HIV ARVs

Avoid strong P-gp inducers: Rifampin, Carbamazepine, St. John's Wort and Tipranavir

A cautionary tale

Combined <50 copies/mL week 24: RAL 84.4%, LPV 90.6% (-6.2%; -11.2 to -1.3)

Reported history of virologic failure

<table>
<thead>
<tr>
<th>Combined studies</th>
<th>RAL</th>
<th>LPV-rit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>85/131</td>
<td>85-96% (84.4-96.4)</td>
</tr>
<tr>
<td>No</td>
<td>32/212</td>
<td>89-94% (87-91.2)</td>
</tr>
</tbody>
</table>


SOF/LDV DDIs with antiretrovirals

- LDV: slow oxidative metabolism
  - Not a CYP substrate in vitro
  - P-gp substrate and inhibitor (intestinal)
- Healthy volunteer studies of LDV±SOF with:
  - RAL (n=30)
  - TDF/FTC/EFV (n=32)
  - TDF/FTC/RPV (n=32)
- No interaction: LDV and RAL; LDV and RPV

**SOF/LDV DDIs with antiretrovirals**

- EFV: ~35% reduction in LDV exposure
  - LDV: no impact of EFV
  - SOF/LDV: 40-98% increase in TFV AUC
  - 90-150% increase in $C_{\text{tau}}$

**3D DDI: RAL, RPV, EFV**

- Healthy volunteer study
  - 3D regimen with RAL, TDF/FTC, RPV 25mg
  - 2D regimen (ABT-450/r, Dasabuvir) with EFV
  - EFV arm discontinued prematurely
  - RPV exposure similar to 75mg (QTc $\uparrow$10s)
  - No significant impact on 3D regimen

**3D DDIs: LPV, ATV, DRV**

- Healthy volunteer study of 3D regimen with:
  - ATV/r 300/100mg QAM or QPM
  - ritomitted if given in AM with 3D regimen
  - DRV/r 800/100mg QAM or QPM or 600/100mg BID
  - ritomitted if given in AM with 3D regimen
  - LPV/r 800/200mg QPM or 400/100mg BID
  - DRV $C_{\text{min}}$ 43-48% lower
  - DRV/r BID with 3D comparable exposure to DRV/r QD
  - DRV/r QD and BID being evaluated in TURQUOISE I
  - Dasabuvir $C_{\text{min}}$ 46% lower with DRV BID (AUC $\downarrow$27%)
Daclatasvir Drug Interactions: Unique Role in Co-infection?

- Substrate of Pgp and CYP3A4
  - Moderate Pgp inhibitor
- ATV/r- DCV 20mg: AUCₜ: 0.70, C₂₄: 1.21
  - 30mg (est): AUCₜ: 1.05, C₂₄: 1.83
- EFV- DCV 120mg: AUCₜ: 1.37, C₂₄: 0.83
  - 90mg (est): AUCₜ: 1.03, C₂₄: 0.62
- TDF- DCV 60mg: AUCₜ: 01.10, C₂₄: 1.17

Phase 3 trial using these adjusted doses with SOF:
ALLY2: NCT02032888

Scorecard: Which DAA regimen with which HAART regimen

<table>
<thead>
<tr>
<th>HAART Regimen</th>
<th>SOF/RBV</th>
<th>SOF/SMV</th>
<th>SOF/LDV</th>
<th>SOF/DCV</th>
<th>3D/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC/EFV</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>TDF/FTC/RPV</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td>DRV/rit</td>
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<tr>
<td>ATV/rit</td>
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<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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</tr>
<tr>
<td>RAL</td>
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<td>✔️</td>
<td>✔️</td>
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<tr>
<td>DTG</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

ATV/r: 100-115% increase in LDV Cmax and AUC

Regimen options for patients who need to switch

- EFV-based regimens
  - Change to RPV-, RAL-, or DTG-based regimens
- Boosted PI regimens
  - DTG (BID if needed)
  - Heavily drug experienced or concern for M184V?
    - TDF/FTC/RPV plus INSTI
  - More extensive HIV resistance
    - Time to get creative!
    - Risk/benefit discussion
      - Use SOF/LDV with DRV/rit?
      - Wait for 3D regimen data with DRV?
A FEW WORDS ON ACCESS AND PROVIDERS

Access: The Good

• SOF has a label indication for co-infection
• Preliminary studies are well underway with promising DAA regimens
  – No specific mention in SOF/LDV label
  – Adequate DDI data available
• To date, HIV co-infection not routinely used as a means for denial
• Patient assistance programs open to HIV+
• ADAP covers new DAAs (varies by state)

Access: The Bad

It’s OK to Limit Who Prescribes HCV Therapy, but Insurers Shouldn’t Be Deciding
It just shouldn’t be that the companies paying for the treatment, on their own, get to decide who the qualified providers are — they’re hardly disinterested enough to make this judgment wisely. —Paul Sax, MD

IDSA, HIVMA Call for State Medicaid Programs to Lift Hepatitis C Prescribing Restrictions from ID and HIV Doctors
Now is not the time to place restrictions on the availability of physicians, especially those with some of the most experience treating this disease. —Barbara Murray, MD, President IDSA
HIV specialists are also well suited to treat co-infected patients and to handle complications that may arise from therapy. Restricting us from providing this care does a great disservice to our patients and to public health. —Joel Gallant, MD, MPH, Chair HIVMA

Access: The Future and Summary

- What impact will the availability of multiple DAA regimens have on cost and access?
- Efficacy is not an issue when considering treatment for HCV in those with HIV
- Keep a pharmacist close by...
- Carefully review HIV treatment history before switching to accommodate HCV therapy
Drug-Drug Interactions and Other Considerations With Direct-Acting Antivirals (DAAs)

Lucas A. Hill, PharmD

Ambulatory Care Pharmacist
University of California San Diego

Learning Objectives

After attending this presentation, learners will be able to:

- Recognize potential drug-drug interactions (DDIs) in simeprevir and sofosbuvir
- Describe the compatibility of soon to be approved DAAs in hepatic impairment
- Recognize potential DDIs with soon to be approved DAAs

Overview

- Review drug interactions with current DAAs simeprevir, sofosbuvir, and ledipasivr
- Discuss sofosbuvir in renal impairment
- Discuss simeprevir in hepatic impairment
- Review drug interactions and required dose adjustments for upcoming DAAs
- Review available data regarding upcoming DAAs in renal and hepatic impairment
Simeprevir PK

- Intake with food increases exposure by about 60%
- Substrate of the intestinal uptake transporter P-glycoprotein (P-gp)
- Distributed to liver by organic anion transporting polypeptide (OATP)
- Metabolized primarily by CYP3A
- Inhibits OATP and P-gp
- Mild inhibitor of intestinal CYP3A and 1A2 (not liver)

Drugs Effect on SMV

<table>
<thead>
<tr>
<th>Decreased Simeprevir concentrations</th>
<th>Anticonvulsants</th>
<th>Antimycobacterials</th>
<th>NNRTIs</th>
<th>Systemic Desamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Rifampin</td>
<td>Efavirenz</td>
<td>Etavirine</td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine</td>
<td>Rifapentine</td>
<td>Nevirapine</td>
<td>Etravirine</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Rifabutin</td>
<td>St. Johns Wort</td>
<td>Tipranavir</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Increased Simeprevir concentrations</th>
<th>Antifungals</th>
<th>Boosted PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Colicidat</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Itraconazole</td>
<td>Milk Thistle</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Ketoconazole</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>Ketoconazole</td>
<td>Verapamil</td>
</tr>
</tbody>
</table>

SMV Effect on Drugs

<table>
<thead>
<tr>
<th>Increased Drug Concentration</th>
<th>Antiarrhythmics</th>
<th>CCB</th>
<th>HMG Co-A Red Inhib.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Amlodipine</td>
<td>Rosuvastatin (10mg)</td>
</tr>
<tr>
<td></td>
<td>Dipyridamole</td>
<td>Diltiazem</td>
<td>Atorvastatin (40mg)</td>
</tr>
<tr>
<td></td>
<td>Ticlopidine</td>
<td>Felodipine</td>
<td>Simvastatin</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
<td>Nicardipine</td>
<td>Pitavastatin</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
<td>Nifedipine</td>
<td>Pravastatin</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
<td>Nisoldipine</td>
<td>Lovastatin</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sildenafil</td>
<td>Midazolam (oral)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sildenafil</td>
<td>Triazolam (oral)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sildenafil</td>
<td>Cisapride</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cilostat</td>
<td>Digoxin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cilostat</td>
<td>Erythromycin</td>
<td></td>
</tr>
</tbody>
</table>
SMV and CSA

- Due to CYP3A4 inhibition of CSA and increase in SMV AUC almost 6-fold, it is not recommended to use CSA and SMV in combination.

SMV and Tacrolimus

- SMV AUC increased 1.85-fold when given with tacrolimus.
- SMV has not been studied with sirolimus – monitor levels when given in combination with SMV.

SMV in renal impairment

- Biliary excretion with less than 1% of drug recovered in urine.
- Mild to moderate renal impairment does not significantly affect PK.
- 62% increase in AUC in severe renal impairment – not considered clinically significant.
- Highly protein bound so unlikely it will be removed by dialysis.
SMV in hepatic impairment

**Figure 1:** Mean (± SD) plasma concentration-time curves for SMV on Day 1 up to 48 hours post-dose in volunteers with normal hepatic function, moderate hepatic impairment and severe hepatic impairment in this study.

<table>
<thead>
<tr>
<th></th>
<th>Least squares means ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate (CTP B) vs. normal</td>
</tr>
<tr>
<td></td>
<td>Severe (CTP C) vs. normal</td>
</tr>
<tr>
<td></td>
<td>Severe vs. moderate</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>1.71 (1.02-2.88)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;24h&lt;/sub&gt;, ng.h/mL</td>
<td>2.44 (1.36-4.38)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Least squares means ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate vs. HCV-infected</td>
</tr>
<tr>
<td></td>
<td>Severe vs. HCV-infected</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>0.93 (0.46-1.87)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;24h&lt;/sub&gt;, ng.h/mL</td>
<td>1.30 (0.53-3.20)</td>
</tr>
</tbody>
</table>

**Simeprevir AE**

- Potential AE related to increased SMV exposure
  - Rash
  - Pruritis
  - Photosensitivity
  - Increased bilirubin
- Strategies for reducing SMV exposure
  - Avoid significant DDI
  - Take medication on an empty stomach
  - Every other day in severe hepatic impairment (induction, adequate levels?)
**Sofosbuvir PK**

- Pro-drug nucleotide analog that gets triphosphorylated in the liver
- Does not undergo traditional hepatic metabolism
- Primary metabolite (GS-331007) undergoes renal elimination via glomerular filtration and active tubular secretion
- Substrate of P-gp and breast cancer resistance protein (BCRP)

---

**Sofosbuvir DDI**

**Decreased Sofosbuvir concentrations**

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Antimycobacterials</th>
<th>Tipranavir/Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Rifampin</td>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Rifapentine</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Rifapentine</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Rifampin</td>
<td></td>
</tr>
</tbody>
</table>

---

**SOF in renal impairment**

*Figure 1. Mean GS-331007 Concentration vs Time in Subjects with Normal Renal Function and All Renal Impairment Groups.*

SOF in renal impairment

Geometric Least-Squares Mean Ratio for AUC Renal Impairment
Group: Normal Renal Function Group (90% Confidence Interval)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mild Impairment</th>
<th>Moderate Impairment</th>
<th>Severe Impairment</th>
<th>ESRD Pre-dialysis</th>
<th>ESRD Post-dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-7977 AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>1.61 (1.10-2.35)</td>
<td>2.06 (1.30-3.29)</td>
<td>2.73 (1.96-3.81)</td>
<td>1.34 (0.88-2.02)</td>
<td>1.35 (0.85-2.34)</td>
</tr>
<tr>
<td>GS-566500 AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>1.61 (1.08-2.38)</td>
<td>2.35 (1.74-3.18)</td>
<td>3.44 (2.41-5.20)</td>
<td>1.87 (1.47-2.39)</td>
<td>3.75 (2.64-5.34)</td>
</tr>
<tr>
<td>GS-331007 AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>1.56 (1.30-1.87)</td>
<td>1.90 (1.52-2.36)</td>
<td>5.56 (2.96-10.43)</td>
<td>4.92 (3.44-7.04)</td>
<td>8.97 (6.35-12.70)</td>
</tr>
</tbody>
</table>


SOF in renal impairment

- Not recommended if eGFR < 30ml/min/1.73m<sup>2</sup> or in ESRD
- Ongoing study evaluating 200mg and 400mg dose in severe renal impairment and ESRD

Ledipasvir PK

- NSSA-Inhibitor
- Primarily eliminated in the feces as unchanged parent drug
- Approx. 1% of drug is eliminated in the urine
- Little to no effect on CYP enzymes
- P-gp and BCRP substrate
- Weak inhibitor of P-gp and BCRP

European Medicine Agency
LDV DDI

- P-gp inducer/inhibitors – similar DDIs to sofosbuvir
- Avoid co-administration with
  - Anticonvulsants – carbamazepine, phenytoin, phenobarbital, oxcarbazepine
  - Antimycobacterials – rifabutin, rifampin, rifapentine
  - St. Johns Wort
- Avoid administration with rosuvastatin
- Monitor digoxin levels
- No significant DDI with CSA or FK

<table>
<thead>
<tr>
<th>P-gp substrates</th>
<th>Colchicine, atorvastatin, simvastatin, pravastatin, lovastatin, digoxin, diltiazem, verapamil, rivaroxaban, methotrexate, anti-neoplastics, cyclosporine, tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCRP substrates</td>
<td>Methotrexate, ciprofloxacin, anti-neoplastics, pravastatin, rosuvastatin, rivaroxaban, AZT, 3TC</td>
</tr>
</tbody>
</table>

LDV and acid reducing agents

- Decreased solubility with increasing pH
- Separate administration with antacids by 4 hours
- H2-receptor antagonists to be administered simultaneously with or 12 hours apart
  - Do not exceed comparable dose of famotidine 40mg daily
- Administer PPI’s simultaneously
  - Do not exceed comparable dose of omeprazole 20mg daily

LDV in hepatic impairment

3D regimen

- Protease inhibitor paritaprevir (ABT-450) with ritonavir co-formulated with NS5A inhibitor ombitasvir (ABT-267)
- Non-nucleoside polymerase inhibitor dasabuvir (ABT-333)

3D DDI – P-gp

![Graph showing effect of 3D DDI on digoxin](image)


3D DDI

- Recommendation likely will be to reduce pravastatin by half and maximum dose of rosvustatin of 10mg

Based on PK study no dose adjustment of warfarin, omeprazole, digoxin, zolpidem, alprazolam, duloxetine, escitalopram, furosemide, methadone, buprenorphine, naloxone

Recommended to avoid with carbamazepine (and likely other CYP inducing anticonvulsants) and gemfibrozil (increased dasabuvir)

Dose adjustments for pravastatin, rosuvastatin, amlodipine
3D and immunosuppressants

- Phase 1 study demonstrated 3-fold increase in CSA half-life and 7-fold increase in FK half-life.
- In Phase II study CSA dose was reduced to 20% of usual daily dose and FK to 0.5mg weekly or 0.2mg every 3 days
- CSA concentrations maintained within desired range, FK dose was 0.5-1mg at 1-2 week intervals for most patients.


Ritonavir

- Substrate of P-gp, CYP3A and 2D6
- Inducer of CYP1A2, 2C8, 2C9, 2C19
- Inhibitor of P-gp, CYP3A, 2D6, MRP1, OATP, BCRP

Avoid co-administration with ritonavir: Alfuzosin, amiodarone, phenytoin, cisapride, diazepam, ziprasidone, triazolam, ergotamine, flecainide, pimozide, ritanserin, simvastatin, lovastatin, voriconazole, rivaroxaban, salmeterol

Use with caution with ritonavir: Fluticasone, budesonide, fentanyl, methadone (monitor), carbamazepine, clarithromycin, digoxin, rifabutin, PDE-5 inhibitors, atorvastatin, rosuvastatin, pravastatin, tacrolimus, cyclosporine, sirolimus, trazodone, oral contraceptives, colchicine, quetiapine

3D in hepatic impairment

- In moderate hepatic impairment ombitasvir, dasabuvir and ritonavir exposure were comparable to controls, ABT-450 AUC was moderately higher at 62%
- In severe hepatic impairment ombitasvir AUC was moderately lower (55%), ritonavir was comparable, ABT-450 and dasabuvir AUC were significantly higher (920% and 320%)
- In severe hepatic impairment dasabuvir half-life was 75% higher and ritonavir 250% higher

**Daclatasvir PK**

- NS5A Inhibitor - once daily
- Minimal renal clearance (5%)
- Not expected to require dose adjustments in hepatic impairment
- Metabolized by CYP3A4, P-gp substrate
- Moderate inhibitor of OATP1B1 and P-gp

**Daclatasvir DDI**

- DCV given with ATV/r (CYP3A inhibitor)
  - decrease to 30mg daily
- DCV given with EFV (CYP3A inducer)
  - increase to 90mg daily
- Consider similar adjustments for other potent CYP3A inhibitors or inducers
DCV in renal impairment

- AUC estimated to increase 1.3, 2.1, and 1.9-fold in ESRD, moderate, or severe renal impairment relative to subjects with normal renal impairment
- Increased exposure is within exposure-safety assessment and no dose adjustments are required


DCV in hepatic impairment


Asunaprevir

- Compatible with ESRD
- Likely not recommended in moderate to severe hepatic impairment
- Metabolized by CYP3A4, substrate of P-gp, OATP1B1
- Weak inducer of CYP3A4, weak inhibitor of P-gp, and moderate inhibitor of CYP2D6


Asunaprevir DDI

- Ketoconazole significantly increased asunaprevir levels
  - Caution with CYP3A4 and P-gp inhibitors
- Asunaprevir is a moderate inhibitor of CYP2D6
  - Substrates include antidepressants, antipsychotics, codeine, dextromethorphan, and others

Eley T, He B, Huang S-P. Effect of Multiple Dose Ketoconazole and the Effect of Multiple Dose Rifampin on the Pharmacokinetics of the HCV NS3 protease inhibitor Asunaprevir.  8th Hepatitis PK Workshop, June 2013.

Asunaprevir in hepatic impairment

Table 4. Comparison of PK Parameters in Subjects with Hepatic Impairment Versus Healthy Control Subjects at Day 7

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Cmax [GMR (90% CI)]</th>
<th>AUCinf [GMR (90% CI)]</th>
<th>Cmin [GMR (90% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh A vs Control</td>
<td>0.16 (0.145, 0.177)</td>
<td>0.16 (0.145, 0.177)</td>
<td>1.59 (0.974, 2.60)</td>
</tr>
<tr>
<td>Child-Pugh B vs Control</td>
<td>0.43 (2.99, 4.47)</td>
<td>2.93 (0.76, 12.45)</td>
<td>11.9 (0.1, 13.7)</td>
</tr>
<tr>
<td>Child-Pugh C vs Control</td>
<td>2.29 (12.6, 41.4)</td>
<td>32.1 (20.8, 49.4)</td>
<td>76.5 (43.4, 120)</td>
</tr>
</tbody>
</table>


Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inhibition</th>
<th>Induction</th>
<th>Substrate</th>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>-</td>
<td>-</td>
<td>P-gp</td>
<td>Not recommended GFR&lt;30</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Moderate CYP3A4, weak CYP3A</td>
<td>P-gp</td>
<td>No adjustment needed</td>
<td>Caution in CTP B and C</td>
<td></td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>Moderate P-gp and OATP</td>
<td>P-gp</td>
<td>No adjustment needed</td>
<td>No adjustment needed</td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Moderate CYP3A4, weak CYP3A4, P-gp</td>
<td>No adjustment needed</td>
<td>No adjustment needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asunaprevir</td>
<td>Weak CYP3A4, P-gp, OATP, BCRP</td>
<td>No adjustment needed</td>
<td>Likely need to avoid in CTP B and C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-D regimen</td>
<td>CYP3A4, 2D6, P-gp, DATP, BCRP</td>
<td>CYP3A4, 2D6, 2C19 (based on ritonavir PK)</td>
<td>Likely no adjustment needed</td>
<td>May need to avoid in severe impairment</td>
<td></td>
</tr>
</tbody>
</table>

Notes

Please note: The case-based presentation slides are intentionally omitted from the course materials so that the case discussions can be spontaneous. Electronic copies of the cases will be available to all participants following the course.
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