DISCLAIMER

Gilead Sciences played no role in the development of this manual. Additionally, the views expressed in this manual do not reflect those of the World Health Organization (WHO), whose normative guidance is cited at various points throughout the manual, unless otherwise explicitly stated through a citation.
The International Association of Providers of AIDS Care (IAPAC) established its African Regional Capacity-Building Hub with a mission to strengthen clinician capacity around HIV, HBV, and HCV clinical management. The Hub’s work is advanced in collaboration with national, regional, and international stakeholders, and through a restricted educational grant from Gilead Sciences.

The Hub is aligned to assist with ongoing efforts to expand access to HBV, HCV, and HIV screening, testing, prevention, care, and treatment on the African continent. The Hub’s 2015-2020 goals include:

- Supporting countries to integrate World Health Organization (WHO), IAPAC, and other relevant normative guidance, including national guidelines, to strengthen their HBV, HCV, and/or HIV responses;
- Increasing clinician capacity to implement HBV, HCV, and/or HIV normative guidance, along their respective continua, in specialized and primary care settings based on needs specifically determined at clinical sites; and
- Promoting continuing education and metrics-based certification as mechanisms to trigger continuing quality improvement, provide quality assurance, and address health workforce retention concerns.

IAPAC is the Hub’s Secretariat, and its association and academic partners are the International Association for the Study of the Liver (IASL), the Makerere University College of Health Sciences (Kampala, Uganda), and the University of Cape Town’s Division of Hepatology (South Africa).
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<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AASLD</td>
<td>American Association for the Study of Liver Disease</td>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
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<td>AE</td>
<td>adverse event</td>
<td>HCV</td>
<td>hepatitis C virus</td>
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<td>ALT</td>
<td>alanine aminotransferase</td>
<td>HCVag</td>
<td>HCV antigen</td>
</tr>
<tr>
<td>APRI</td>
<td>aspartate aminotransferase to platelet ratio index</td>
<td>HCW</td>
<td>healthcare worker</td>
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<td>ART</td>
<td>antiretroviral therapy</td>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>aspartate transaminase</td>
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<td>branched DNA</td>
<td>IAPAC</td>
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<td>baseline</td>
<td>IASL</td>
<td>International Association for the Study of the Liver</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
<td>IDSA</td>
<td>Infectious Disease Society of America</td>
</tr>
<tr>
<td>CrCl</td>
<td>creatinine clearance</td>
<td>IDU</td>
<td>injection drug use</td>
</tr>
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<td>CROI</td>
<td>Conference on Retroviruses and Opportunistic Infections</td>
<td>IFN</td>
<td>interferon</td>
</tr>
<tr>
<td>CSW</td>
<td>commercial sex worker</td>
<td>IgG core Ab</td>
<td>immunoglobulin G core antibody</td>
</tr>
<tr>
<td>CTPB</td>
<td>Child-Tucotte-Pugh class B</td>
<td>IgM core Ab</td>
<td>immunoglobulin M core antibody</td>
</tr>
<tr>
<td>CTPC</td>
<td>Child-Tucotte-Pugh class C</td>
<td>LDV</td>
<td>ledipasvir</td>
</tr>
<tr>
<td>DAA</td>
<td>direct-acting antiviral</td>
<td>MPGN</td>
<td>membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>DCV</td>
<td>daclatasvir</td>
<td>MSM</td>
<td>men who have sex with men</td>
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<td>DSV</td>
<td>dasabuvir</td>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>EASL</td>
<td>European Association for the Study of the Liver</td>
<td>peg-IFN</td>
<td>pegylated-interferon</td>
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<tr>
<td>eGFR</td>
<td>epidermal growth factor receptor</td>
<td>PI</td>
<td>protease inhibitor</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
<td>PTV</td>
<td>paritaprevir</td>
</tr>
<tr>
<td>EOT</td>
<td>end of treatment</td>
<td>PWID</td>
<td>people who inject drugs</td>
</tr>
<tr>
<td>EOTR</td>
<td>end of treatment response</td>
<td>RAV</td>
<td>resistance-associated variant</td>
</tr>
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<td>ESKD</td>
<td>end-stage kidney disease</td>
<td>RBV</td>
<td>ribavirin</td>
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<td>GGT</td>
<td>gamma-glutamyl transferase</td>
<td>RdPp</td>
<td>RNA-dependent RNA polymerase</td>
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<td>GT</td>
<td>genotype</td>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>GT1a</td>
<td>genotype 1, subtype 1a</td>
<td>RT-PCR</td>
<td>reverse transcription polymerase chain reaction</td>
</tr>
<tr>
<td>GT1b</td>
<td>genotype 1, subtype 1b</td>
<td>RTV</td>
<td>ritonavir</td>
</tr>
<tr>
<td>GT2</td>
<td>genotype 2</td>
<td>SIM, or SMV</td>
<td>simeprevir</td>
</tr>
<tr>
<td>GT3</td>
<td>genotype 3</td>
<td>SOF</td>
<td>sofosbuvir</td>
</tr>
<tr>
<td>GT4</td>
<td>genotype 4</td>
<td>SVR</td>
<td>sustained virologic response</td>
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<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

Acronyms:
- AASLD: American Association for the Study of Liver Disease
- AE: adverse event
- ALT: alanine aminotransferase
- APRI: aspartate aminotransferase to platelet ratio index
- ART: antiretroviral therapy
- AST: aspartate transaminase
- bDNA: branched DNA
- BL: baseline
- BMI: body mass index
- CrCl: creatinine clearance
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- CTPC: Child-Tucotte-Pugh class C
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- DNA: deoxyribonucleic acid
- DSV: dasabuvir
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- eGFR: epidermal growth factor receptor
- ELISA: enzyme-linked immunosorbent assay
- EOT: end of treatment
- EOTR: end of treatment response
- ESKD: end-stage kidney disease
- GGT: gamma-glutamyl transferase
- GT: genotype
- GT1a: genotype 1, subtype 1a
- GT1b: genotype 1, subtype 1b
- GT2: genotype 2
- GT3: genotype 3
- GT4: genotype 4
- HBV: hepatitis B virus
- HCC: hepatocellular carcinoma
- HCV: hepatitis C virus
- HCVag: HCV antigen
- HCW: healthcare worker
- HIV: human immunodeficiency virus
- HIVAg: HIV antigen
- IAPAC: International Association of Providers of AIDS Care
- IASL: International Association for the Study of the Liver
- IDSA: Infectious Disease Society of America
- IDU: injection drug use
- IFN: interferon
- IgG core Ab: immunoglobulin G core antibody
- IgM core Ab: immunoglobulin M core antibody
- LDV: ledipasvir
- MPGN: membranoproliferative glomerulonephritis
- MSM: men who have sex with men
- OBV: ombitasvir
- PCR: polymerase chain reaction
- peg-IFN: pegylated-interferon
- PI: protease inhibitor
- PTV: paritaprevir
- PWID: people who inject drugs
- RAV: resistance-associated variant
- RBV: ribavirin
- RdPp: RNA-dependent RNA polymerase
- RNA: ribonucleic acid
- RT-PCR: reverse transcription polymerase chain reaction
- RTV: ritonavir
- SIM, or SMV: simeprevir
- SOF: sofosbuvir
- SVR: sustained virologic response
- WHO: World Health Organization
INTRODUCTION

Purpose
The purpose of this manual is to provide trainers with guidance and tips for leading a training using the IAPAC African Regional Capacity-Building Hub’s HCV Clinical Management curriculum.

Training Package
The HCV Clinical Management training package consists of:

- Train-the-Trainer Manual
- Presentation slides for each module
- Participant handouts (e.g., guidelines, case studies)

Target Audience
The target audiences for trainings using this manual and the HCV Clinical Management curriculum are physicians and nurses, as well as health educators from a variety of settings, including:

- Healthcare facilities and clinics
- Medical and nursing schools
- Community-based organizations
- Other facilities serving people living with or at risk for HCV
LEARNING CYCLE

Kolb’s experiential learning cycle has four phases: concrete experience which leads the learner to make observations and reflections based on their experiences. These observations and reflections then inform the conceptualizations and generalizations made by the learner on the subject matter. The conceptualizations and generalizations are then tested by learners using actual experimentation. New insights from experimentation form the basis of new concrete experience, thus making a full cycle.

In general teaching and learning aims at effective change in three domains:

1. Cognitive (knowledge) “Head”
2. Psychomotor (skills) “Hand”
3. Affective (attitudes) “Heart”

FIGURE 1. Kolb’s Experiential Learning Cycle

KNOWLEDGE RETENTION

In general, humans remember:

- 20% of what they hear,
- 40% of what they see, and
- 80% of what they discover by themselves.

Research shows that in general adults to do not concentrate beyond 40 minutes hence the need to have a variety of experiential learning designs.

NOTES FOR TRAINERS

Keep all of this in mind as you prepare your training: adult participants need to hear, reflect, interact, and practice new knowledge and skills; long lectures are not the most helpful methods for teaching adults.

Good training helps participants discover what they already know, and validates their own experiences and knowledge, as well as provides new information. Finding ways to train participants through a combination of lectures, plenary discussions, small group work, and individual reflection – maximizes learning potential for participants.

KEY STEPS IN TRAINING DESIGN

1) Context Analysis. An analysis of the organizational needs or other reasons the training is desired. Consider:

- a. What are the needs of the participants that the training will address?
- b. Why is the training program seen as the recommended solution to an information gap?
- c. What is the history of the institution with regard to staff in-service training?
- d. Who will decide when the training should happen?
2) User Analysis. This analysis seeks to determine:

a. For whom is the training relevant?
b. What is the participants’ level of existing knowledge on the core content?
c. How much time are the participants (or their employers) able to make available for the training?
d. What kind of expertise or competencies should the trainers possess?

3) Content Analysis. Analysis of material relevant to the training. We seek to answer:

a. What knowledge or information is currently used on the job?
b. What new knowledge, skills, or values are required to fill the information gap?
c. What is the general learning style of the participants?
d. What learning approaches and methodologies are suitable for the content and learning style of participants?

4) Training Suitability Analysis. Training is one of several solutions to service delivery gaps. Therefore we seek to answer:

a. How will the training link to broader strategies for change?
b. With whom should we share the draft curriculum for critical feedback?
c. How will effective training result in a return of value to the organization that is greater than the initial investment to produce or administer the training?
d. What materials and resource do we need to mobilize given budget provisions and limitations?

5) Setting Objectives. Although some trainers use teaching objectives that focus on what the trainer plans to do, it is recommended to use learning objectives in order to focus on the learner outcome.

An example of a teaching objective may be: “To update, reinforce, and provide new information regarding the clinical management of HCV.”

To modify this into a learning objective, start with the phrase: “At the conclusion of this activity, participants should be able to…” and then state the measurable activities the participants will be able to do, for example “describe the therapeutic options to reduce HCV-related morbidity and mortality.” Use specific action verbs (behavioral terms) to state cognitive outcomes:

<table>
<thead>
<tr>
<th>KNOWLEDGE</th>
<th>COMPREHENSION</th>
<th>APPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Define</td>
<td>Explain</td>
<td>Apply</td>
</tr>
<tr>
<td>List</td>
<td>Express</td>
<td>Employ</td>
</tr>
<tr>
<td>Recognize</td>
<td>Describe</td>
<td>Demonstrate</td>
</tr>
<tr>
<td>Record</td>
<td>Discuss</td>
<td>Illustrate</td>
</tr>
<tr>
<td>Repeat</td>
<td>Identify</td>
<td>Interpret</td>
</tr>
<tr>
<td>State</td>
<td>Restate</td>
<td>Perform</td>
</tr>
<tr>
<td></td>
<td>Translate</td>
<td>Practice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use</td>
</tr>
</tbody>
</table>

6) Monitoring and Evaluation. We seek to answer:

a. How will the training’s efficacy be evaluated during and after the training?
b. How will we monitor and evaluate the manner the trainees have adopted or applied their learning?

NOTES FOR TRAINERS

A few hours of thinking through all of the above listed questions will improve your ability to plan a training session that provides real benefit to individual participants, the group as a whole, and the community. Do not skip this important step!
WORKING DEFINITIONS

Training design: A complete and thorough description and “fleshing out” of the training that contains rationale, objectives, content/core topics, training methods, time, evaluation tools, facilitating roles and responsibilities, and materials and other resources needed.

Training: An educational process involving the creation and acquisition of knowledge, skills, and attitudes.

Curriculum: A general description of the training or course that contains the:

a. aim(s)/goal(s)/purpose
b. specific objectives
c. course content
d. training methods/pedagogy
e. timeframe for the training
f. criteria for training evaluation

Syllabus: Contents of a course or training arranged according to a flow.

Module: A series of related activities responding to a particular set of objectives that can be undertaken independently; this may be one component of a curriculum.

NOTES FOR TRAINERS

A few final thoughts:

- It is important to always keep in mind your final goal: What is it you want the participants to have gained by the end of the training? What change in knowledge/attitudes/behavior do you want them to exhibit?
- Knowing how much to include in a training is a matter of experience. It is often useful to know the key items that you want to present, and make sure that there is time to address those items. Additionally, it is useful to have other topics for discussion or presentation prepared that may or may not be used depending on how quickly or slowly the group moves.
- Be ready to spend more time than you planned on key topics if it is clear the group needs more time to work through ideas or needs more time to practice; it is better to do a few things well than to speed through the entire curriculum and “lose” the group. If most of the group seems to understand and is ready to move on, but a few participants still seem confused or unsure, meet with them over breaks or after the training to spend more time with them to ensure that everyone understands the key concepts and skills.
- Be flexible to modify the training based on the group’s interest and learning priorities while keeping the end goal in sight. When the training diverges from the planned approach, assess whether the diversion is helpful in reaching the overall objective of the training. If it is just an interesting conversation but does not contribute to reaching the overall objective, suggest that it be moved to a lunch discussion.
Planning Ahead

Administrative Support: The course will need to be organized (advertise, receive registrations, find and book venue, etc.) and course materials will need to be prepared. This may take up to 10 days.

Facilitator versus Co-Facilitators: One facilitator is recommended per 60 in-service training participants for a one-day course. However, if the training agenda is split over two days held consecutively, it is recommended that two facilitators conduct the course.

Training Venue:
- You will require a room to hold up to 60 participants, with participants sitting in groups (preferably in groups of 5) around tables.
- You will require audiovisual equipment for use of PowerPoint presentation.
- You may print the slides onto overhead transparencies if you do not have PowerPoint projector capabilities.
- Organize payment for venues (if required).
- Familiarize yourself with the venue facilities (air-conditioning/heating, lighting, PowerPoint projector, tea and coffee facilities, toilets, parking, etc.).

Geo-Mapping Trainings and Trainees: We seek to geo-map the geographic reach of Hub trainings. We ask trainers to provide detailed updates after each training session regarding numbers of individuals trained accompanied by relevant non-identifying demographic information, including trainees’ academic credentials, practice settings, geographic locations (city/province), overall patient caseloads, and HCV-specific caseloads. Along with the date and location of the training session, the demographic information should be emailed to AfricanHub@iapac.org with the subject line “HCV Trainees.”

Costing: Determine whether you need to pay for venue hire, audiovisual equipment hire, catering, and printing. In some instances, such costs may be recouped by charging trainees an administrative fee.

Publicity: A draft promotional flyer has been supplied for you to modify. Sample text for email announcements will be provided.

Registration: You will need email or postal addresses of all participants in order to send pre-reading materials. Additionally, you may collect such information such as job title, contact details, and prior experience (and food preferences).

Invoicing: If participants are required to pay for the course, they will require an invoice for processing payment of the administrative fee.

Catering: It is recommended that morning coffee/tea, lunch, and afternoon coffee/tea are provided, in addition to water. You should check food preferences prior to placing a catering order.
ONCE REGISTRATIONS HAVE BEEN RECEIVED

Confirmations:

☐ Email participants to confirm their registration has been received and that they will receive pre-reading material at least 1 week (preferably 2 weeks) prior to the course.
☐ Organize name tags.
☐ Send all participants the pre-reading material at least 1 week (preferably 2 weeks prior to the course).
☐ Order a sufficient supply of training manuals. This can be done by emailing AfricanHub@iapac.org with the email heading “HCV Hub Supplies Request.”

Printing Course Materials: This manual includes a series of handouts, including the training agenda, case studies, and self-assessment questions.

☐ Each document should be printed and collated by placing a colored piece of paper/divider at the end of each document to distinguish between documents.
☐ Do not forget to print out the evaluation form and course certificates (provided), too.

ON THE TRAINING DAY

You will require:

☐ All module slides
☐ Name tags
☐ Training agenda
☐ Training manuals
☐ Handouts (e.g., guidelines)
☐ Evaluation forms
☐ Certificates of completion
## TRAINING AGENDA

IAPAC AFRICAN REGIONAL CAPACITY-BUILDING HUB: HCV IN-SERVICE TRAINING

**NOTE:** Trainers may make adjustments to the training agenda, IAPAC encourages trainers to ensure that all elements of the curriculum are covered by the conclusion of the training.

### DATE:

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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</thead>
<tbody>
<tr>
<td>8:00 AM–9:00 AM</td>
<td>Registration/Check-In</td>
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<tr>
<td>9:00 AM–9:15 AM</td>
<td>Welcome, Introductions, and Training Overview</td>
</tr>
<tr>
<td>9:15 AM–9:30 AM</td>
<td>Module 1: Virology of Hepatitis C Virus Infection</td>
</tr>
<tr>
<td>9:30 AM–10:00 AM</td>
<td>Module 2: Screening and Testing for and Assessment of HCV Infection</td>
</tr>
<tr>
<td>10:00 AM–10:45 AM</td>
<td>Module 3: The HCV Treatment/Cure Landscape</td>
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<tr>
<td>10:45 AM–11:15 AM</td>
<td>Break</td>
</tr>
<tr>
<td>11:15 AM–11:45 AM</td>
<td>Module 4: Chronic HCV Treatment Recommendations</td>
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</table>

### FACILITY, CITY, COUNTRY:

<table>
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<tr>
<th>Time</th>
<th>Activity</th>
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</thead>
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<tr>
<td>11:45 AM–12:15 PM</td>
<td>Module 5: HCV Management in Specific Populations</td>
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<tr>
<td>12:15 PM–12:45 PM</td>
<td>Question and Answer Session</td>
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<tr>
<td>12:45 PM–1:45 PM</td>
<td>Lunch</td>
</tr>
<tr>
<td>1:45 PM–3:00 PM</td>
<td>Learning Activity: Case Study Application</td>
</tr>
<tr>
<td>3:00 PM–3:30 PM</td>
<td>Summary and Evaluation</td>
</tr>
<tr>
<td>3:30 PM</td>
<td>Adjourn</td>
</tr>
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</table>
TRAINER INTRODUCTION

INSTRUCTIONS TO FACILITATOR

1) Distribute course materials and name tags to participants.

2) Trainer introduction: Introduce yourself (and other facilitators if appropriate) and detail your background and experience. Alternatively, you may participate in the group introduction and icebreaker.

3) Participant introductions and icebreakers: There are many choices when it comes to icebreakers. You may have your own preferences.

4) Participants’ expectations: Ask the group to openly provide feedback on the four ‘G’s’:
   - Gives (what participants can give to the course)
   - Gains (what they hope to gain from the course)
   - Ghastlies (what they hope does not happen in the course (e.g., too simple, too advanced, not relevant, etc.))
   - Ground rules (what rules can the group agree upon (e.g., one person talks at a time, no single person to dominate discussion, etc.)

   You should write these down on butcher’s paper or on a whiteboard (or transparency) so you can regularly refer to them during the course and assess if the course is meeting their needs.

5) Discuss course objectives and outline of the one-day training agenda.

6) Address housekeeping issues – toilets, breaks, coffee/tea/water, or any other issues.
MODULE 1
VIROLOGY OF HEPATITIS C VIRUS

TRAINER GUIDE

Time Required:
Approximately 30 minutes

Supporting Materials:
PowerPoint Slides

Learning Objectives:
1. Understand the global burden of HCV disease
2. Describe the hepatitis C virus (virological characteristics, genotype distribution)
3. List HCV transmission risks
4. Explain the HCV lifecycle, specifically viral proteins and enzymes
Hepatitis C Virus

Single-stranded, positive sense, RNA virus
- Flavivirus family

No RNA polymerase proofreading ability
- Forms heterogeneous viral populations or quasispecies

Half-life: 2.3 hours

Daily production: 10^{11} virions

36000-variant acid polysaccharide

Great genetic diversity
- Six genotypes: 1, 2, 3, 4, 5, 6 and 7 subtypes: a, b, c, etc.

Risk Factors for HCV infection

- Injecting drug use
- Blood/blood products <1992 or where blood safety is inadequate
- Unsafe medical or dental interventions e.g. unsafe injection use
- Traditional practices
- Tattooing and body piercing using unsterilized equipment

Global HCV Genotype Distribution

- Identifies the distribution of HCV genotypes worldwide

Train-The-Trainer Manual: HCV Clinical Management
**HCV Lifecycle Overview**

**Lifecycle: Viral Polyprotein**

The viral RNA undergoes translation resulting in a single viral polyprotein.

**Viral Enzymes**

- **NS3/4A protease**: assists in the downstream cleavage of viral peptides. It also has ability to cleave and inactivate host proteins that aid in antiviral activity (IRF-3)
- **NS5B RNA-dependent RNA polymerase (RdRp)**: facilitate viral replication by copying a positive strand RNA into negative strand intermediate (a template for more viral RNA genomes)
- **NS5B RdRp**: lacks proof reading capabilities and therefore mutations of HCV genome occurs at a rate of $10^{-4}$ per nucleotide
- **NS5A "replicase"**: assists in viral replication and viral assembly.
MODULE 2
SCREENING AND TESTING FOR AND ASSESSMENT OF HCV INFECTION

TRAINER GUIDE

Time Required:
Approximately 30 minutes

Learning Objectives:
1. Explain HCV screening as a public health priority
2. Identify who should be screened for HCV
3. List HCV diagnostic tools
4. Describe HCV genotyping
5. Define the role of liver biopsy
6. Discuss non-invasive tests

Supporting Materials:
PowerPoint Slides
Case Study (refer to Learning Activities section)
Sub-Saharan Africa Who Should be Screened for HCV?

Remains unclear:
- Persons with persistently abnormal ALT levels
- Recipients of transfusions (prior to ??)
- Persons with unrecognized occupational exposures e.g. HCWs
- Exposure to unsafe injection or medical practices
- Children born to HCV-positive women
- HIV-positive persons
- ? Traditional practices
- Persons who ever injected illegal drugs

Hepatitis C Virus: Diagnostic Testing

<table>
<thead>
<tr>
<th>DIAGNOSTIC TEST TYPE</th>
<th>Serologic</th>
<th>Virologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of detection</td>
<td>Antibodies</td>
<td>Virus</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>&gt; 95%</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Specificity</td>
<td>Variable</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Detection postexposure</td>
<td>2-6 months</td>
<td>2-5 weeks</td>
</tr>
<tr>
<td>Use</td>
<td>Screening</td>
<td>Confirmation</td>
</tr>
</tbody>
</table>

HCV Antibody Testing

ELISA screening tests
- Detect circulating HCV antibodies
- Sensitivity: 83% to 100%
- Positive predictive value
  - 90% with risk factors and elevated ALT
  - 50% without risk factors and normal ALT

<table>
<thead>
<tr>
<th>Positive Tests</th>
<th>Negative Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous, present infection</td>
<td>Healthy non-infected</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>Normal individuals</td>
</tr>
<tr>
<td>HIV positive</td>
<td>HIV negative</td>
</tr>
</tbody>
</table>

Severely thrombocytopenic patients
- Immunosuppressed patients
- Transplantation recipients
- Patients with chronic renal failure on dialysis
- HIV positive
HCV Confirmation Test
Detection of HCV RNA
- All persons with positive anti-HCV antibody test must undergo additional testing for the presence of the HCV itself to determine whether current infection is present and whether there is an indication for treatment.
- HCV PCR is the most common method to detect viral RNA.
- It is also used to quantify the virus for treatment monitoring purpose.
- HCV PCR is not widely accessible and costs $200 USD per test.

A great need exists for an affordable:
- Point Of Care HCV Viral load or HCV Ag test (with good sensitivity)
- Flexible PCR platforms (Multi-test: HBV, HIV, HCV)

Molecular Testing
Recommended for all individuals who test positive for anti-HCV antibody
Should also be done in high risk groups who present with acute hepatitis

<table>
<thead>
<tr>
<th>Assay Method</th>
<th>Method</th>
<th>Test Duration</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobas® 5800 System</td>
<td>PCR</td>
<td>1 hour</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Cobas® 5800 System</td>
<td>PCR</td>
<td>1 hour</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Cobas® 5800 System</td>
<td>PCR</td>
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<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Cobas® 5800 System</td>
<td>PCR</td>
<td>1 hour</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Cobas® 5800 System</td>
<td>PCR</td>
<td>1 hour</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
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<td>PCR</td>
<td>1 hour</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Cobas® 5800 System</td>
<td>PCR</td>
<td>1 hour</td>
<td>99%</td>
<td>99%</td>
</tr>
</tbody>
</table>

Determination of HCV Genotype
HCV genotype — currently:
- Determines choice of regimen
- Predictor of response
- Influence duration of therapy

ATTENTION: should have genotype determined prior to initiating therapy

Preliminary genetic testing potentially eliminates need for genotyping.
Fibrosis Assessment = Disease Severity

Liver Biopsy  Serum Biomarkers  FibroScan

Liver Biopsy
- Remains the gold standard
- Invasive
- Only test that can accurately assess:
  - Severity of inflammation
  - Degree of fibrosis

Noninvasive Serum-Based Biomarkers

FibroTest
- Combines 6 markers: 
  a2-macroglobulin, haptoglobin, GGT, total bilirubin, apolipoprotein A1

FibroScan
- Combines 6 markers: 
  a2-macroglobulin, haptoglobin, GGT, total bilirubin, apolipoprotein A1

AFTB
- AST to platelet ratio index

Fornier Score index
- Age, platelet count, GGT, cholesterol

PI-R-4
- Combines 4 markers: platelets, ALT, AST, age
Transient Elastography
Noninvasive Alternative to Assess Liver Fibrosis

Elastography
• Ultrasound transducer probe induces elastic wave through the liver
• Velocity of the wave is evaluated in a region located from 2.5 to 6.5 cm below the skin surface

Liver biopsy is able to examine 1/50,000 of the liver, elastography is able to examine 1/1000 of the liver
Potential confounders: excess adiposity, cirrhosis, cholestasis, significant inflammation
Sensitivity is improved when combined with noninvasive biomarker scores

• Examination time: <10 minutes
• Median value: 35 successful acquisitions
TRAINER GUIDE

Time Required:
Approximately 45 minutes

Learning Objectives:
1. Describe the concept that achieving an SVR equates to a cure
2. Explain how SVR in patients with chronic HCV results in long-term clinical benefits
3. Review the first 2 decades of therapy with Peg-IFN and Ribavirin
4. Understand that interferon based therapy is unrealistic for many parts of Africa
5. Identify where in the lifecycle of HCV the new DAA therapies act
6. List the guiding principles of all oral DAA therapy
7. Express the indications for DAA therapy
8. Define adverse effects of specific DAA agents
9. Discuss how to avoid/manage drug-drug interactions

Supporting Materials:
PowerPoint Slides
Case Study (refer to Learning Activities section)
Aim of HCV Treatment = Cure

SVR is Durable

SVR (Cure) and Improved Outcomes

- Durable
- Improved quality of life
- Leads to improved histology
- Leads to clinical benefits
- Reduced risk of death
- Decreases decompensation
- Decreases risk of hepatocellular carcinoma


*With permission from John Wiley & Sons, Inc.*
**SVR (Cure) Improves Health**

**Advanced Fibrosis**
- Multicenter study
  - 5 hospitals (Toronto, Canada)
  - 100 patients with HCV
  - IFN regimens 1990-2003
  - Advanced fibrosis or cirrhosis
  - Median follow-up = 8.4 yrs.

**Early-stage disease**
- Delta hepatic manifestations
  - Health-related quality of life

**HCV Therapy in Patients with Marked Fibrosis?**

- 4,401 patients with chronic HCV from Rome since 1982
- History of inactive disease
- Observation for 29 years

- SVR 12% (82% was lost to follow-up)
- SVR 20% (90% was lost to follow-up)
- SVR 30% (88% was lost to follow-up)

**PEG-IFN + RBV**

- Treatment era of Pegylated-Interferon and Ribavirin
- Summary (1980 – 2013):
  - SVR rates increase over time
  - But 30-50% of patients do not achieve SVR

---

Train-The-Trainer Manual: HCV Clinical Management

25
DAAs in 2015/2016

<table>
<thead>
<tr>
<th>Protease inhibitors</th>
<th>Polymerase inhibitors</th>
<th>NS5A inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>Peginterferon</td>
<td>Daclatasvir</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Buparlisib</td>
<td>Velpatasvir</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Regorafenib</td>
<td>Ledipasvir</td>
</tr>
</tbody>
</table>

The Treatment Landscape in 2015

- Sofosbuvir + daclatasvir
- Ledipasvir + ribavirine
- Ombitasvir

Oral DAA Regimens – Guiding Principles

- Combine drugs from different classes
  - Protease (NS3/4A) inhibitors
  - Polymerase (NS5B) inhibitors
  - NS5A inhibitors

- Multiple drugs combined to produce greater efficacy and reduce risk of viral resistance (not unlike HIV ART)
### Indications for HCV Treatment

<table>
<thead>
<tr>
<th>Treatment priority</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with advanced fibrosis or cirrhosis (F3 or F4)</td>
<td>&gt; 60% chance of cure</td>
</tr>
<tr>
<td>Patients with HIV/HCV coinfection or multi-drug resistant HCV</td>
<td>50% chance of cure</td>
</tr>
<tr>
<td>Patients with HCV genotype 1a, 2a, 3a or 4a, no other structural or functional abnormalities</td>
<td>50% chance of cure</td>
</tr>
<tr>
<td>Patients with HIV/HCV coinfection or multi-drug resistant HCV</td>
<td>50% chance of cure</td>
</tr>
<tr>
<td>Patients with HCV genotype 1a, 2a, 3a or 4a, no other structural or functional abnormalities</td>
<td>50% chance of cure</td>
</tr>
</tbody>
</table>

### Treatment with Intent to Prevent Transmission to Others
- Active injection drug users
- Incarcerated people
- Men who have sex with men with high-risk sexual practices
- Patients on long-term haemodialysis
- HCV-infected women of childbearing age who wish to be pregnant

### Adverse Effects of DAAs
- **LED**: Fatigue, Nausea, Headache
- **SOF**: Fatigue, Nausea
- **Olaplex**: Fatigue
- **Ribavirin**: Nephrotoxic anaemia, Acute
- **Daclatvir**: Nephrotoxic anaemia, Acute
TRAINER GUIDE

Time Required:
Approximately 30 minutes

Learning Objectives:
1. Describe the indications for HCV treatment
2. Identify what clinical data are needed to make an HCV treatment decision
3. Explain HCV treatment options for non-cirrhotic, cirrhotic, treatment-naïve, and treatment-experienced patients
4. State selected data that underpins HCV treatment options
5. Recognize what contributes to HCV treatment failures

Supporting Materials:
PowerPoint Slides
Case Study (refer to Learning Activities section)
## Indications for HCV Treatment

Treatment prioritization needs to be applied in resource-limited settings.

<table>
<thead>
<tr>
<th>Treatment priority</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment can be deferred</td>
<td></td>
</tr>
<tr>
<td>Treatment should be prioritized</td>
<td></td>
</tr>
<tr>
<td>Prioritize treatment</td>
<td></td>
</tr>
<tr>
<td>Patients with cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Patients with severe liver disease</td>
<td></td>
</tr>
<tr>
<td>Patients with decompensated liver disease</td>
<td></td>
</tr>
<tr>
<td>Patients with other serious comorbid conditions</td>
<td></td>
</tr>
<tr>
<td>Patients with high-risk behavior (e.g., intravenous drug use)</td>
<td></td>
</tr>
<tr>
<td>Patients with HIV coinfection</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from: CmR, Treatment Recommendations HCV, April 2012

## Important Data in Choosing a Regimen

**HCV treatment history**
- Drug history and ribavirin regimen?
- Previous protease inhibitor?

**Fibrosis stage**?
- Options for fibrosis assessment
  - If cirrhosis, is it decompensated?

[Link to http://www.hepinfo.org](http://www.hepinfo.org)

## Non-Cirrhotic

*Treatment-Naive or Peg-IFN/Ribavirin-Experienced Genotype 1, 4, 5*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HCV Genotype</th>
<th>1a</th>
<th>1b</th>
<th>1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-INF + RBV</td>
<td>12 weeks, no RVR</td>
<td>12 weeks, no RVR</td>
<td>12 weeks, no RVR</td>
<td></td>
</tr>
<tr>
<td>PEG-INF + RBV</td>
<td>24 weeks, no RVR</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>12 weeks, no RVR</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>SVR + RBV</td>
<td>12 weeks, no RVR</td>
<td>12 weeks, no RVR</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>SBP + SVR</td>
<td>12 weeks, no RVR</td>
<td>12 weeks, no RVR</td>
<td>Not recommended</td>
<td></td>
</tr>
</tbody>
</table>

*[^1](#)

Adapted from: CmR, Treatment Recommendations HCV, April 2012.
Ledipasvir/Sofosbuvir for
12 weeks in GT4 or 5 HCV

Open-label, single-arm study; 12 wks LDV/SoF 90/400 mg QD
Treatment-naïve or experienced with GT4 or 5 HCV, cirrhosis permitted

<table>
<thead>
<tr>
<th>SVR12, % (n/N)</th>
<th>Genotype 4</th>
<th>Genotype 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>93 (41/45)</td>
<td>95 (63/66)</td>
</tr>
<tr>
<td>Treatment-naïve</td>
<td>93 (17/18)</td>
<td>95 (31/33)</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>93 (23/25)</td>
<td>95 (31/31)</td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>93 (13/14)</td>
<td>97 (10/10)</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>90 (20/22)</td>
<td>94 (6/6)</td>
</tr>
</tbody>
</table>

Hamzi et al. 2019, NEJM; 2016, Hepato 2020

Compensated Cirrhosis
*Treatment-Naïve or PEG-IFNRBV/5b in Experienced Genotype 1, 4, 5

<table>
<thead>
<tr>
<th>Regimen</th>
<th>12 wks</th>
<th>18 wks</th>
<th>24 wks</th>
<th>36 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SoF</td>
<td>12 wks</td>
<td>18 wks</td>
<td>24 wks</td>
<td>36 wks</td>
</tr>
<tr>
<td>LDV/SoF + RBV</td>
<td>36 wks</td>
<td>Not recommended</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ledipasvir/Sofosbuvir + RBV in Patients
with Child B/C Liver Cirrhosis

CTP B

Comparative efficacy between SOLAR-1 and SOLAR-2 studies

Train-The-Trainer Manual: HCV Clinical Management
### Treatment-Naïve or Peg-IFN/Ribavirin-Experienced GT 2 or 3

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis (Child-Pugh A)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G72</td>
<td>G73</td>
</tr>
<tr>
<td>SOF + RBV†</td>
<td>12 wks</td>
<td>24 wks</td>
</tr>
<tr>
<td>SOF + DCV</td>
<td>12 wks</td>
<td>no RBV</td>
</tr>
<tr>
<td></td>
<td>no RBV</td>
<td>no RBV</td>
</tr>
</tbody>
</table>

†DOS, dosages; RBV, ribavirin; DCV, daclatasvir.
†Sofosbuvir 100 mg once daily for 22 weeks.

### BOSON Study
SVR with SOF-Based Treatment in GT3 by Treatment History and Cirrhosis Status

![Bar chart showing SVR outcomes for different treatment regimens and cirrhosis statuses.]

### Daclatasvir + Sofosbuvir in Treatment-Naïve and -Experienced GT 3 HCV

**ALLY-3 study**
- Treatment-naïve and experienced
- Prior sofosbuvir included
- Prior DAA inhibitors excluded
- Cirrhosis: 21%
- 2 open-label cohorts
- Phase III

**Regimen:**
- Daclatasvir + sofosbuvir once daily for 22 weeks

![Graph showing SVR rates for different treatment regimens and cirrhosis statuses.]

MODULE 5
HCV MANAGEMENT IN SPECIFIC POPULATIONS

TRAINER GUIDE

Time Required:
Approximately 30 minutes

Learning Objectives:
1. Understand the changing nature of difficult to treat and difficult to cure HCV-infected patients in the DAA era
2. Explain the difference between compensated and decompensated cirrhosis
3. Define chronic kidney disease and HCV-related impaired renal function
4. Identify management options for HCV/HIV coinfection
5. Describe the emerging problem of NS5A treatment failures

Supporting Materials:
PowerPoint Slides
Case Study (refer to Learning Activities section)
Changing Paradigm of Difficult to Cure/Treat HCV

<table>
<thead>
<tr>
<th>FAST PEG-INF/R/RBV/AMRN ERA</th>
<th>PRESENT DAA ALL ORAL ERA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIFFICULT TO CURE</strong></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Advanced/decompensated cirrhosis</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>Genotype 3, advanced fibrosis/cirrhosis</td>
</tr>
<tr>
<td>High viral load</td>
<td>DAA failure</td>
</tr>
<tr>
<td>≤300 ILT</td>
<td></td>
</tr>
<tr>
<td>Treatment-intolerant</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td>No transplant</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
</tr>
<tr>
<td><strong>DIFFICULT TO TREAT</strong></td>
<td></td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>Chronic kidney disease/ESRD</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>Potential Drug/Drug Interactions</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>Risk of missed treatment</td>
</tr>
<tr>
<td>(Ac or Multivitamin inpatient)</td>
<td></td>
</tr>
<tr>
<td><strong>DIFFICULT TO ACCESS</strong></td>
<td></td>
</tr>
<tr>
<td>No access to new DAA therapies</td>
<td></td>
</tr>
</tbody>
</table>

Special Populations
- Compensated and decompensated cirrhosis
- Impaired renal function
- HCV/HIV co-infection
- DAA failure

Patients with Cirrhosis
- Patients with compensated disease (Childs-Pugh A, MELD < 15) achieve similar SVR rates to those without cirrhosis
- SVR may prevent further decompensation
- Decompensation associated with reduced response to therapy
- Important to recognize clinical, laboratory, and radiological signs of decompensation:
  - Worsening jaundice, ascites, INR increasing
Compensated Cirrhosis

- Recommendations in Module 4
- SVR rates almost equal to that of non-cirrhotics

Effect of Treatment Duration and RBV with LDV/SOF in GT 1 Cirrhosis

Effect of Treatment Duration with OLV/PTV/RTV + DSV in GT-1 Cirrhosis
### Daclatasvir and Sofosbuvir ± Ribavirin in GT1

Treatment naive or treatment experienced

<table>
<thead>
<tr>
<th>Population</th>
<th>GT1</th>
<th>All Genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

African Regional Capacity-Building Hub | IAPAC

### Decompensated Cirrhosis: AASLD/IDSA Recommendations

*Refer to an experienced HCV practitioner (ideally liver transplant center)*

<table>
<thead>
<tr>
<th>Population</th>
<th>DCE ± SOF</th>
<th>DCE + RBV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1</td>
<td>low dose</td>
<td>low dose</td>
</tr>
<tr>
<td></td>
<td>8 wk</td>
<td>12 wk</td>
</tr>
<tr>
<td>GT1 +/SOF failure</td>
<td>not recommended</td>
<td>not recommended</td>
</tr>
</tbody>
</table>

*RBV dose of 500 mg/day, increased as tolerated

### Decompensated Cirrhosis: GT 1 and 4 Trial Data

Hepatitis and Renal Disease

- HCV infection can cause renal disease or be associated with renal disease
  - Mixed cryoglobulinemia
  - Membranoproliferative glomerulonephritis (MPGN)
  - Polycystic kidneys
- Possible HCV associated
  - Focal segmental glomerulosclerosis
  - Membranous or Membranoproliferative glomerulonephritis
- HCV and diabetes association
- HCV infection independently associated with increased mortality in hemodialysis patients
- Increased rate of progression to cirrhosis and risk of hepatocellular cancer

OMVIPRTV/RTV + DSV ± RBV in Treatment-Naive, Non-Cirrhotic GT1 with CKD

- Treatment arm of multinational, open-label, phase 3 study in patients with HCV GT1 with HCV MDR (n=133)
- RBV (1000 mg/day) for 12 weeks and OMV/PR/RTV (200 mg/day) for 12 weeks
- DSV 50/50 mg: patients reaching post-treatment week 4
- SVR2endpoint: 12 weeks

Hematologic Effect of RBV and Overall Safety

- RBV dose interruption in 7/13 GT1a pts (n=1 in first 8 weeks)
- No hematological effects, no discontinuations, or significant changes in lab or renal function reported
- 3 serious adverse events attributable to study treatment
- Most labs resolved to normal
### Dosing Recommendations in Renal Impairment

- **CBV/TPV/RTV + 3TC:** No dose adjustment required with mild, moderate, or severe renal impairment (CrCl 30-59 mL/ min).  
- **LDV/SOF and SMV + SOF:** No dose adjustment required with mild or moderate renal impairment (CrCl ≥ 30 mL/ min).  
- **DCV:** Use of 200 mg (50 mL/ min).  
- **RBV:** Dose adjustment required for CrCl < 50 mL/ min.

### HCV/HIV Coinfection

- No longer considered difficult to cure.  
- Same recommendations as in HCV mono-infected patients.  
- Consider drug-drug interactions.  
  - Avoid combination of RBV and tenofovir if CrCl < 40 mL/ min or if receiving tenofovir with RTV boosted PI.  
- When LDV/SOF and tenofovir are co-administered with ART, monitor for nephrotoxicity.  
- Adjust RTV if receiving a boosted PI with LDV/TPV/RTV + DSV.  
- Adjust DCV with atazanavir/RTV, efavirenz, or darunavir.

### LDV/SOF for 12 Weeks in HCV/HIV Coinfection

- GT 1 or 4 HCV, 30% with compensated cirrhosis, 5% treatment-experienced
**OMV/PTV/RTV + DSV + RBV for 12 vs 24 Weeks in GT1 HCV/HIV Coinfection**

- 100% HCV treatment-naive patients in 12-week arm, 95% in 24-week arm
- 39% HCV/HIV-1 patients with MM/MS 8/14 Mexico

**SOF + DCV in HCV/HIV Coinfection**

- 100% HCV treatment-naive patients in 12-week arm, 95% in 24-week arm
- 39% HCV/HIV-1 patients with MM/MS 8/14 Mexico

**Treatment Failure with NS5A Inhibitor AASLD/IDSA Recommendations for GT-1**

- If minimal liver disease, defer treatment, pending further data
- If cirrhotic or treatment otherwise urgent, resistance testing for ns3a that confer decreased susceptibility to NS5a PIs, NS5as recommended
- If both NS5A and NS3 RAMs detected, treatment within clinical trial recommended

<table>
<thead>
<tr>
<th>Treatment Failure</th>
<th>OMV + SOF</th>
<th>OMV/PTV + DCV</th>
<th>OMV/PTV/RTV + DCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted Outcome</td>
<td>100%</td>
<td>95%</td>
<td>90%</td>
</tr>
</tbody>
</table>

AASLD/IDSA HCV guidelines
Learning Activity Modules 2–5

Case Study Application. Teams of two to four trainees are given three patient case studies and asked to apply the information learned from Modules 2-5. This team activity is followed by a whole class discussion of each team’s conclusions and responses to the case study questions. This activity requires approximately one hour and 15 minutes to complete.

Case Study 1

A 56-year-old man, after complaining of unexplained fatigue, is noted on routine evaluation to have an abnormal liver profile (see below). He has no background medical history of note. In 1984 he was involved in a motor vehicle accident with polytrauma and received several units of blood as a result of a pelvic fracture. He is a businessman, who does not smoke but drinks about 1 glass of wine per day. He uses no substances. His laboratory results are as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Ref. range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>141 mmol/l</td>
<td>135 — 147</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.6 mmol/l</td>
<td>3.3 — 5.3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>89 µmol/l</td>
<td>64 — 104</td>
</tr>
<tr>
<td>Bilirubin total</td>
<td>13 µmol/l</td>
<td>0 — 21</td>
</tr>
<tr>
<td>Bilirubin conjugated</td>
<td>4 µmol/l</td>
<td>0 — 6</td>
</tr>
<tr>
<td>Albumin</td>
<td>36g/l</td>
<td>35 — 52</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>62 U/l</td>
<td>40 — 120</td>
</tr>
<tr>
<td>γ-Glutamyl Transferase (GGT)</td>
<td>75 U/l</td>
<td>0 — 60</td>
</tr>
<tr>
<td>Alanine transaminase (ALT)</td>
<td>98 U/l</td>
<td>5 — 40</td>
</tr>
<tr>
<td>Aspartate transaminase (AST)</td>
<td>60 U/l</td>
<td>5 — 40</td>
</tr>
<tr>
<td>White cell count</td>
<td>4.60 x 10⁹/l</td>
<td>4 — 10</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>14.3 g/dl</td>
<td>13 — 17</td>
</tr>
<tr>
<td>MCV</td>
<td>97.6 fl</td>
<td>79 — 99</td>
</tr>
<tr>
<td>Platelets</td>
<td>131 x 10⁹/l</td>
<td>137 — 373</td>
</tr>
<tr>
<td>Int. normalized ratio (INR)</td>
<td>1.19</td>
<td></td>
</tr>
</tbody>
</table>

Further workup demonstrated the following:

- Hep A IgM/IgG – negative
- Hepatitis B surface antigen – negative
- Hepatitis B core IgG – positive
- Hepatitis B surface antibodies <10 IU/ml
- Hepatitis C antibody – positive
- HIV Ag/Ab combination assay – non-reactive
- Hepatitis C PCR – positive
- Hepatitis C viral load – 7470000 IU/ml
  Log value – 6.9
- Hepatitis C genotype – 1a
An ultrasound of his abdomen found his liver size is within normal limits of 14cm however with an irregular outline and a coarse echotexture. The PV is patent and measure 10.8mm with flow towards the liver. The hepatic veins and IVC are patent. No parenchymal masses are identified. There is no dilation of the biliary tree. The spleen is moderately enlarged at 12cm. Both kidneys appear normal. No ascites seen.

The patient underwent liver biopsy, which demonstrated a METAVIR score of F4 (fibrosis) with a necro-inflammatory score of A2.

Low power H&E demonstrating portal tract with moderate inflammation and mild interface hepatitis with few lobular necro-inflammatory foci

BSR stain demonstrating bridging fibrosis with incipient cirrhosis

QUESTIONS

1. What is the likely mode of acquisition of hepatitis C in this patient?
2. How would you describe his hepatitis C viral serology?
3. What non-viral treatment management measures would you advise the patient?
4. Are any other investigations required in this patient?
5. Would you advise this patient to consider treatment, if so, why?
6. What treatment options would you consider?
7. What duration of treatment would you advise?
8. Would you add Ribavirin to the regimens you advised?
9. If the patient achieves SVR, what would your long-term management strategy be?
Case Study 2

A 49-year-old man is HIV/HCV-coinfected. He has been on ART for several years with a fully suppressed HIV viral load and a CD4 count of >500 cells/mm³. As part of his HIV care, he was screened for hepatitis B and C a few years ago and noted to be positive for hepatitis C. He used pegylated interferon and ribavirin, but had no change in HCV viral load at week 12 so treatment was abandoned. He also experienced severe side effects including mild depression. His current ART regimen includes tenofovir, emtricitabine, and raltegravir. He is not diabetic but has mild hypertension, managed with perindopril. He is overweight with a BMI of 30. He also takes Simvastatin 20mg daily, prescribed several years ago. He now consults you about his HCV. His laboratory results are as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Ref. range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>138 mmol/l</td>
<td>135 — 147</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.9 mmol/l</td>
<td>3.3 — 5.3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>138 μmol/l</td>
<td>64 — 104</td>
</tr>
<tr>
<td>Bilirubin total</td>
<td>21 μmol/l</td>
<td>0 — 21</td>
</tr>
<tr>
<td>Bilirubin conjugated</td>
<td>7 μmol/l</td>
<td>0 — 6</td>
</tr>
<tr>
<td>Albumin</td>
<td>37 g/l</td>
<td>35 — 52</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>115 U/l</td>
<td>40 — 120</td>
</tr>
<tr>
<td>γ-Glutamyl Transaminase (GGT)</td>
<td>96 U/l</td>
<td>0 — 60</td>
</tr>
<tr>
<td>Alanine transaminase (ALT)</td>
<td>115 U/l</td>
<td>5 — 40</td>
</tr>
<tr>
<td>Aspartate transaminase (AST)</td>
<td>118 U/l</td>
<td>5 — 40</td>
</tr>
<tr>
<td>White cell count</td>
<td>6.8 x 10⁹/l</td>
<td>4 — 10</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13.8 g/dl</td>
<td>13 — 17</td>
</tr>
<tr>
<td>MCV</td>
<td>100.6 fl</td>
<td>79 — 99</td>
</tr>
<tr>
<td>Platelets</td>
<td>256 x 10⁹/l</td>
<td>137 — 373</td>
</tr>
<tr>
<td>Int. normalized ratio (INR)</td>
<td>1.08</td>
<td></td>
</tr>
</tbody>
</table>

Further workup demonstrated the following:

- Hep A IgM – **negative**
- Hep A IgG – **positive**
- Hepatitis B surface antigen – **negative**
- Hepatitis B core IgG – **negative**
- Hepatitis B surface antibodies **616 IU/ml**
- Hepatitis C antibody – **positive**
- Hepatitis C PCR – **positive**
- Hepatitis C viral load – **13 700 000 IU/ml**
  - Log value – 8.1
- Hepatitis C genotype – **4a**

An ultrasound of his abdomen found his liver size is normal with increased echogenicity (fatty change). The PV, HV, and IVC are patent with normal flow. No parenchymal masses are identified. The spleen and kidneys are normal. The patient undergoes liver biopsy, which demonstrates moderate simple fatty change. METAVIR scoring is assessed as A1 necro-inflammation and F2 fibrosis.

**QUESTIONS**

1. What were the likely factors for this patient failing therapy with PEG-IFN and ribavirin?
2. What advice would you give this patient in terms of his need for therapy now?
3. Are any further investigations required in this patient?
4. What therapy options/regimens would you consider and advise?
5. What duration of therapy would you advise?
6. Would you add ribavirin to the treatment regimen(s) above?
7. What implications does his polypharmacy have for therapy?
PATIENT EDUCATION

What is hepatitis C?

- Hepatitis C is a liver disease caused by the hepatitis C virus (HCV).
- Approximately 25% of people clear the virus after initial infection. However, in 75% of cases, it becomes a chronic infection and treatment is necessary.
- HCV is the most common cause of chronic hepatitis, which can lead to more serious problems including cirrhosis (scarring of liver), liver failure, and liver cancer.
- Worldwide, about 150 million people are chronically infected with HCV, and more than 350,000 people die every year from related liver diseases.
- Many people do not have symptoms and do not know they are infected with HCV.

How is HCV spread?

- HCV is spread through direct blood-to-blood contact with an infected person.
- The most common means of infection is needles shared for injection drug use, tattoos, body piercing, etc.
- Before 1990, the virus was spread through blood transfusions.
- Sexual and mother-to-child transmission are rare.

Who is at risk of getting HCV infected?

Those at risk of getting HCV infected include people who:

- were born between 1945 and 1975 (age group with the highest risk);
- have come into contact with the blood of another person through the use of unsterilized needles for medical or dental procedures, tattoos, or injection drug use;
- share personal articles (razors, toothbrushes, scissors, nail clippers) with an HCV-infected person;
- were born or lived in countries where HCV infection is common;
- received a blood transfusion before 1990;
- are healthcare workers and/or have exposure to blood in the workplace;
- have unprotected sexual activity – if there is blood exchange with an infected person (less than 5% risk in heterosexual, monogamous relations); and
- were born to a mother with HCV (less than 5% risk).

What are the symptoms of HCV infection?

- Symptoms may not appear for years after a person is infected.
- Some patients experience fatigue, itchy skin, and pain in the right upper abdomen.
- As the disease progresses, there is severe liver damage and patients experience swelling of abdomen and feet, jaundice, nausea, bruising, and confusion or disorientation.

Is HCV a preventable disease?

There is currently no vaccine for HCV, but it can be easily prevented. Individuals can reduce their risk of HCV infection by adopting the following practices:

- Not sharing needles or other drug-related equipment;
- Making sure that the equipment used for tattooing, piercing, or acupuncture is sterile (the safest way is to go to a professional);
- Wearing protective medical gloves and handling used needles with care in a healthcare facility where contact with someone else’s blood or needle is possible; and
- Not engaging in high-risk behavior.

To prevent the spread of the virus to others, people infected with HCV should not:

- Donate blood;
- Share razors, scissors, nail clippers, or toothbrushes; and
- Share needles or other drug-related equipment.
If a woman is pregnant and has concerns about spreading HCV to her baby, she should talk to her doctor.

Although sexual transmission is rare, people who are infected should inform their sexual partners that they have HCV and take necessary precautions.

Medication also helps reduce the risk of passing HCV on to others so it is important for people to take it as prescribed.

**How is HCV infection diagnosed?**

HCV infection is diagnosed through blood tests.

**Is there a treatment for HCV infection?**

HCV is a curable disease.

Approximately 25% of people clear the virus on their own. However, in 75% of cases, it becomes a chronic infection and treatment is necessary. Current HCV treatments are more than 90% effective in clearing the virus completely, which translated into a cure.

**What else can people do to live well living with HCV?**

It is important for people living with HCV to:

- Get vaccinated against hepatitis A and hepatitis B;
- Implement lifestyle changes, such as maintaining a healthy body weight, eating a well-balanced diet, exercising regularly, quitting smoking, and avoiding alcohol and high-risk behaviors;
- Know that no alternative therapies – including herbal remedies, homeopathic medicines, and minerals – have been proven safe and effective for HCV treatment; and
- Inform their healthcare provider of any medication taken for other conditions because some medications may affect the outcome of HCV treatment (for example, some drugs are harmful to the liver).