TRAIN-THE-TRAINER MANUAL

HCV CLINICAL MANAGEMENT

AFRICAN REGIONAL CAPACITY-BUILDING HUB

IAPAC

Supported through a restricted educational grant from Gilead Sciences.

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.

PREFACE

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).

IAPAC INTERNATIONAL ASSOCIATION OF PROVIDERS OF AIDS CARE

IASL International Association for the Study of the Liver

University of Cape Town • iYunivesithi yaseKapa • Universiteit van Kaapstad

CONTENTS

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
CROI	Conference on Retroviruses and Opportunistic Infections
CSW	commercial sex worker
CTPB	Child-Tucotte-Pugh class B
CTPC	Child-Tucotte-Pugh class C
DAA	direct-acting antiviral
DCV	daclatasvir
DNA	deoxyribonucleic acid
DSV	dasabuvir
EASL	European Association for the Study of the Liver
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

ADULT LEARNING

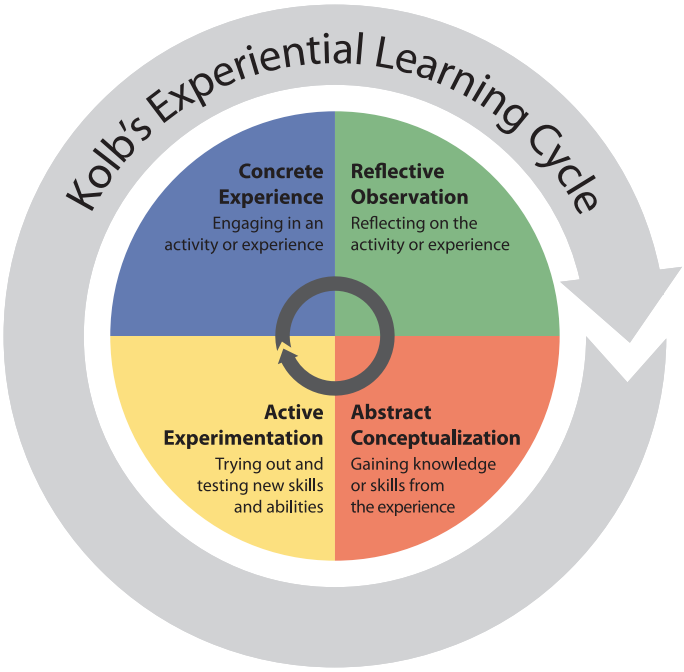
LEARNING CYCLE

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:

KNOWLEDGE	COMPREHENSION	APPLICATION
Define	Explain	Apply
List	Express	Employ
Recognize	Describe	Demonstrate
Record	Discuss	Illustrate
Repeat	Identify	Interpret
State	Restate	Perform
	Translate	Practice
		Use

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.

TRAINING LOGISTICS

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:

FACILITY, CITY, COUNTRY:

8:00 AM–9:00 AM	Registration/Check-In
9:00 AM–9:15 AM	Welcome, Introductions, and Training Overview
9:15 AM–9:30 AM	**Module 1: Virology of Hepatitis C Virus Infection**
9:30 AM–10:00 AM	**Module 2: Screening and Testing for and Assessment of HCV Infection**
10:00 AM–10:45 AM	**Module 3: The HCV Treatment/Cure Landscape**
10:45 AM–11:15 AM	Break
11:15 AM–11:45 AM	**Module 4: Chronic HCV Treatment Recommendations**
11:45 AM–12:15 PM	**Module 5: HCV Management in Specific Populations**
12:15 PM–12:45 PM	**Question and Answer Session**
12:45 PM–1:45 PM	Lunch
1:45 PM–3:00 PM	**Learning Activity: Case Study Application**
3:00 PM–3:30 PM	**Summary and Evaluation**
3:30 PM	Adjourn

TRAINER INTRODUCTION

Time Required:
Approximately 15 minutes

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':

- **G**ives (what participants can give to the course)
- **G**ains (what they hope to gain from the course)
- **G**hastlies (what they hope does not happen in the course (e.g., too simple, too advanced, not relevant, etc.)
- **G**round 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

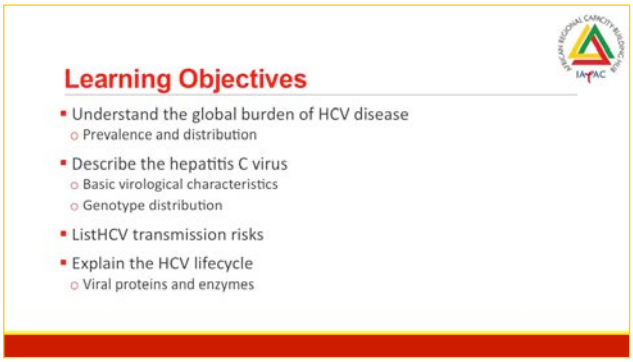
VIROLOGY OF HEPATITIS C VIRUS

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



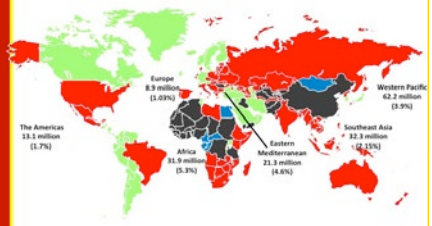
Estimated Global HCV Prevalence

170 million people

- Estimates are derived from a meta-analysis of data from 232 studies published between 1997 and 2007 and NHANES data up to 2010. Point prevalence estimates are calculated using regional population age weights.

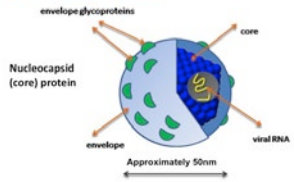
Adapted from Hanafiah KM et al. Hepatology. 2013

Global Burden of HCV Disease



Farci P, et al. Semin Liver Dis. 2000;20:103-126.
Wasley A, et al. Semin Liver Dis. 2000.

HCV Viral Structure



Hepatitis C Virus

Single-stranded, positive sense, RNA virus
- *Flaviviridae* family

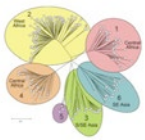
No RNA polymerase proofreading ability
- Forms heterogeneous viral populations or quasispecies

Half-life: ~2.7 hours

Daily production: 10^{12} virions

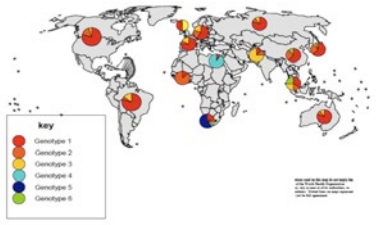
3000-amino acid polyprotein

Great genetic diversity
- Six genotypes: 1,2,3,4,5,6; >80 subtypes: a, b, c, etc.



Choo QL, et al. Science. 1989;244:359-362.

Global HCV Genotype Distribution

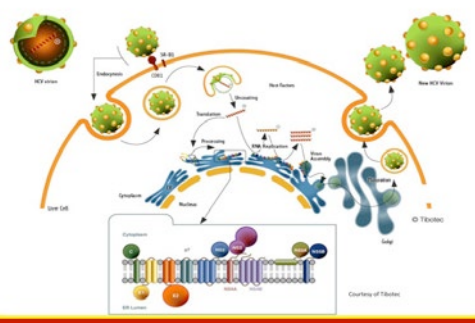


Hoofnagle J. Hepatology 2002; 36: S21

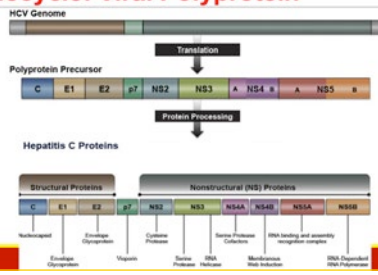
Risk Factors for HCV infection

- 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
- Needle stick injuries (healthcare workers)
- Perinatal/mother to child
- Haemodialysis
- Sexual transmission (notably men who have sex with men)

HCV Lifecycle Overview



Lifecycle: Viral Polyprotein



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

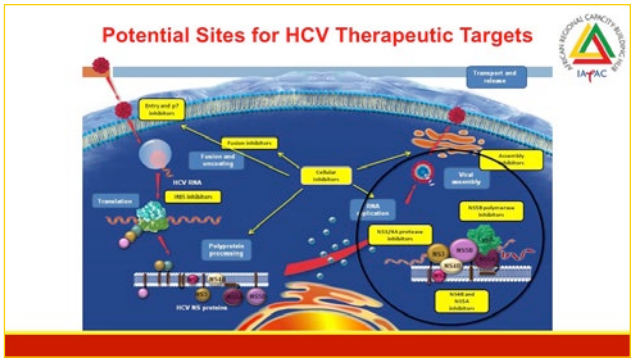
Viral Enzymes

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.


Potential Sites for HCV Therapeutic Targets
Transport and release
Entry and pH inhibitors
Fusion and uncoating
Fusion inhibitors
Cellular inhibitors
Assembly inhibitors
Viral assembly
HCV RNA
Translation
IRES inhibitors
RNA replication
NS5B polymerase inhibitors
NS3/4A protease inhibitors
Polyprotein processing
NS5B
NS4B
NS5A
NS4B and NS5A inhibitors
HCV NS proteins

MODULE 2

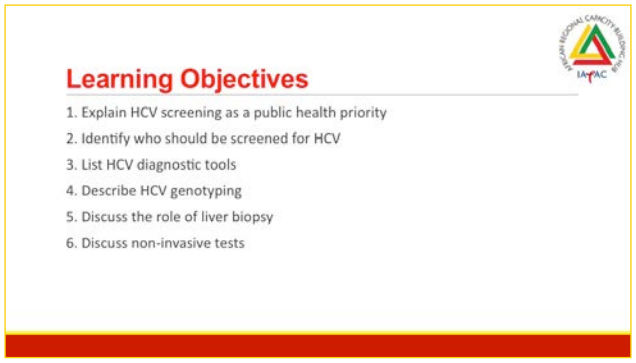
SCREENING AND TESTING FOR AND ASSESSMENT OF HCV INFECTION

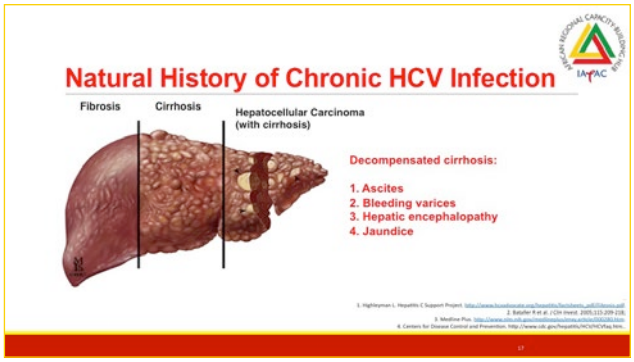
TRAINER GUIDE

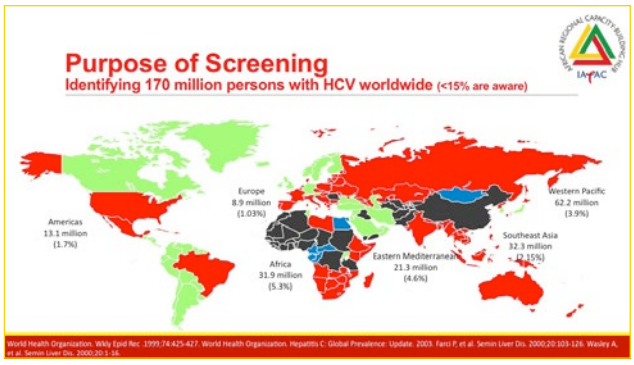
Time Required:
Approximately 30 minutes

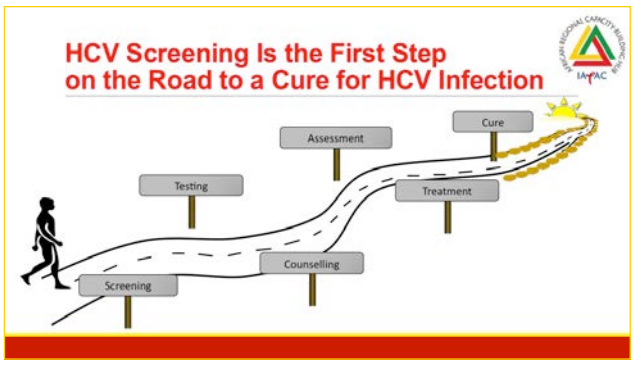
Learning Objectives:
1. Explain HCV screening as a public health priority
2. Identify who should be screened for HCV
3. List HCV diagnostic tools
4. Describe HCV genotyping
5. Define the role of liver biopsy
6. Discuss non-invasive tests

Supporting Materials:
PowerPoint Slides
Case Study (refer to Learning Activities section)




Natural History of Chronic HCV Infection
Fibrosis
Cirrhosis
Hepatocellular Carcinoma
(with cirrhosis)
Decompensated cirrhosis:
1. Ascites
2. Bleeding varices
3. Hepatic encephalopathy
4. Jaundice


Purpose of Screening
Identifying 170 million persons with HCV worldwide (<15% are aware)
Americas
13.1 million
(1.7%)
Europe
8.9 million
(1.03%)
Africa
31.9 million
(5.3%)
Eastern Mediterranean
21.3 million
(4.6%)
Southeast Asia
32.3 million
(2.15%)
Western Pacific
62.2 million
(3.9%)


HCV Screening Is the First Step
on the Road to a Cure for HCV Infection
Screening
Testing
Counselling
Assessment
Treatment
Cure

Who to Screen?

3 approaches

- **Population screening, including antenatal**
- **Risk-factor based screening e.g., PWID, MSM, prisoners**
- **Birth cohort screening**

- No current universal screening program
- Risk based screening: population dependent
- Birth cohort - in USA and Japan

Risk Factors: Who to Screen?

Parenteral	• IDU • Nasal cocaine • Transfusions • Needle stick injury • Tattoos • Body piercing • Manicures • Household items • Hemodialysis
Sexual	• Multiple partners • Traumatic • HIV (+) • Use of a CSW • Rectal contact • MSM
Perinatal	• High viral load • HIV (+)

USA: Who Should Be Tested for HCV?

CDC

- Everyone born 1945-1965 (one-time)
- Persons who ever injected illegal drugs
- Persons who received clotting factor concentrates produced before 1987
- Chronic (long-term) hemodialysis
- Persons with persistently abnormal ALT levels
- Recipients of transfusions or organ transplants prior to 1992
- Persons with recognized occupational exposures
- Children born to HCV-positive women
- HIV-positive persons

USPSTF Grade B Recommendations*

- Everyone born from 1945 through 1965 (one-time)
- Past/present injection drug use
- Sex with an IDU; other high-risk sex
- Blood transfusion prior to 1992
- Persons with hemophilia
- Longterm hemodialysis
- Born to HCV-infected mother
- Incarceration
- Intranasal drug use
- Receiving unregulated tattoo
- Occupational percutaneous exposure
- Surgery before universal precautions implementation

* Only pertains to persons with normal liver enzymes; if elevated liver enzymes need HBV and HCV testing

Smith et al. Ann Intern Med 2012; 157:817-822. Moyer et al. Ann Intern Med

Sub-Saharan Africa
Who Should be Screened for HCV?

Remains unclear

- Persons with persistently abnormal ALT levels.
- Recipients of transfusions (prior) to ???
- Persons with recognized 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

	DIAGNOSTIC TEST TYPE	
Specifications	**Serologic**	**Virologic**
Mode of detection	Antibodies	Virus
Sensitivity	> 95%	> 98%
Specificity	Variable	> 98%
Detection postexposure	2-6 months	2-6 weeks
Use	Screening	Confirmation

HCV Antibody Testing

ELISA screening tests
Detect circulating HCV antibodies
Sensitivity: 97% to 100%

Positive predictive value
- 95% with risk factors and elevated ALT
- 50% without risk factors and normal ALT

False Positives More Likely in:	False Negatives More Likely in:
Previous cleared infection	Severely immunosuppressed patients
Autoimmune disease	Transplantation recipients
HIV positive	Patients with chronic renal failure on dialysis
	HIV positive

Carithers RL Jr, et al. Semin Liver Dis. 2000;20:159-171.
Pawlotsky JM. Hepatology. 2002;36(suppl 1):S65-S73.

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 ≥100 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 group who present with acute hepatitis

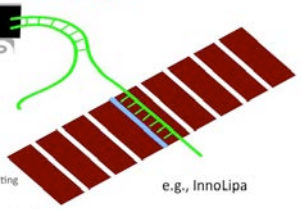
Assay (Manufacturer)	Method	IU/mL Conversion Factor, copies/mL	Dynamic Range, IU/mL	FDA Approved
Amplicor (Roche Molecular Systems)	Manual RT-PCR	0.9	600-500,000	Yes
COBAS Amplicor HCV Monitor V2.0 (Roche Molecular Systems)	Semiautomated RT-PCR	2.7	600-500,000	Yes
VERSANT HCV RNA 3.0 Assay (bDNA)	Semiautomated bDNA signal amplification	5.2	615-7,700,000	Yes
LCx HCV RNA Quantitative Assay (Abbott Diagnostics)	Semiautomated RT-PCR	3.8	25-2,830,000	No
SuperQuant (National Genetics Institute)	Semiautomated RT-PCR	0.4	50-1,470,000	No
COBAS TaqMan HCV Test (Roche Molecular Systems)	Semiautomated RT-PCR	N/A	43-69,000,000	Yes
Abbott RealTime (Abbott Diagnostics)	Semiautomated RT-PCR	N/A	10-100,000,000	Yes

Determination of HCV Genotype

HCV genotype – currently:

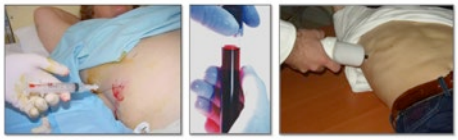
- Determines choice of regimen
- Predictor of response
- Influence duration of therapy

All patients should have genotype determined prior to initiating therapy



Pan-genotypic treatment potentially eliminates need for genotyping

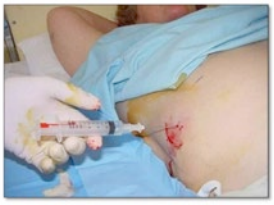
Fibrosis Assessment = Disease Severity



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 5 markers: α_2-macroglobulin, haptoglobin, GGT, total bilirubin, apolipoprotein A1

FibroSpect II
- Combines 3 markers: α2-macroglobulin, hyaluronic acid, tissue inhibitor of metalloproteinase-1

APRI
- AST-to-platelets ratio index

Forns fibrosis index
- Age, platelet count, GGT, cholesterol

FIB-4
- Combines 4 markers: platelets, ALT, AST, age

Transient Elastography
Noninvasive Alternative to Assess Liver Fibrosis

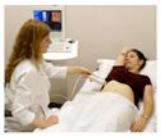
Elastography

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

Liver biopsy is able to examine 1/50,000 of the liver, elastography is able to examine 1/500 of the liver

Potential confounders: visceral adiposity, steatosis, cholestasis, significant inflammation

Sensitivity is improved when combined with noninvasive biomarker scores



- Examination time <10 minutes
- Median value: 10 successful acquisitions

MODULE 3

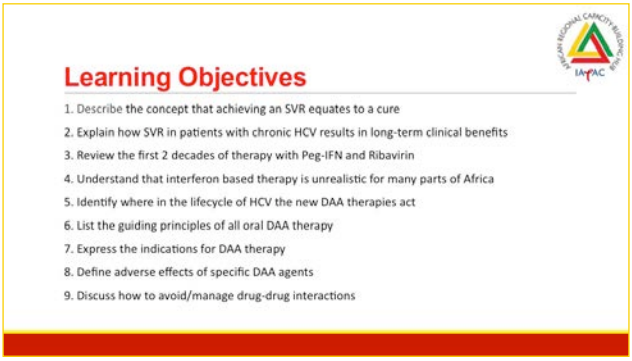
HCV TREATMENT/CURE LANDSCAPE

TRAINER GUIDE

Time Required:
Approximately 45 minutes

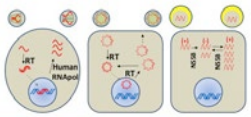
Learning Objectives:
1. Describe the concept that achieving an SVR equates to a cure
2. Explain how SVR in patients with chronic HCV results in long-term clinical benefits
3. Review the first 2 decades of therapy with Peg-IFN and Ribavirin
4. Understand that interferon based therapy is unrealistic for 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

HCV life Cycle favors resistance development not persistence



	HIV	HBV	HCV
Stable genome	Provirus	cccDNA	(none)
Virion NA polymerase	Host RNApol	HBV RT	HCV NS5B
Error-prone replications per cell	One	Multiple	Multiple
Plasticity of genome	High	Constrained	Very high
Recombination	Common	Common	Rare

SVR is Durable

"These patients should be considered as cured"

99.1% undetectable

Independent of population
- Elevated ALT
- Persistently normal ALT
- Immunocompromised

Independent of treatment
- INF monotherapy
- INF/RBV
- PEG/RBV/DAA

Swain et al. Gastro 2010;139:1593-1601
Butter K et al. Ailment Pharmacol Ther 2013 Jul;38(2):118-29

SVR (Cure) and Improved Outcomes

SVR
- Durable
- Improved quality of life
- Leads to improved histology
- Leads to clinical benefits
  - Reduced risk of death
  - Decreases decompensation
  - Prevents de novo esophageal varices
  - Decreases risk of hepatocellular carcinoma

Bruno S. et al. Hepatology. 2010;51:2069-2076. Veldt BJ, et al. Ann Intern Med. 2007;147:677-684.
Mallyn S. et al. Gastroenterology. 2008;135:821-829.

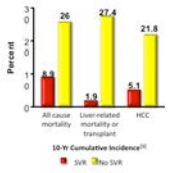
SVR (Cure) Improves Health

Advanced fibrosis

- Multicenter study[1]
  - 5 hospitals (Europe, Canada)
- 530 patients with HCV
  - IFN regimens 1990-2003
  - Advanced fibrosis or cirrhosis
  - Median follow-up: 8.4 yrs

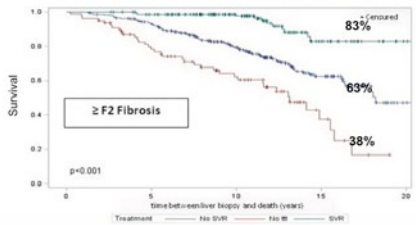
Early-stage disease

- Extra-hepatic manifestations[2]
- Health-related quality of life[3]



1. van der Meer AJ, et al. JAMA. 2012;308:2584-2593. 2. van der Meer AJ. Expert Rev Gastroenterol Hepatol. 2015;9:559-566.
3. Younossi Z, et al. Clin Gastroenterol Hepatol. 2014;12:1349-1359.

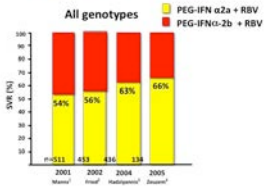
HCV Therapy in Patients with Marked Fibrosis?



4,293 patients with chronic HCV from Rennes since 1992
biopsy at baseline, observation for 20 years in n = 1,381 (52% GT1)

Jézéquel et al., EASL 2015, #P0709

PEG-IFN + RBV

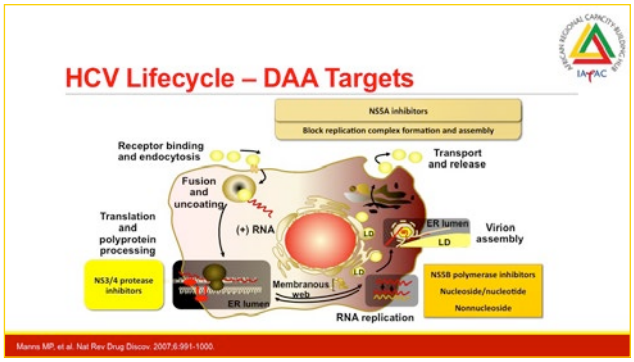


Treatment era of Pegylated-Interferon and Ribavirin summary (1989 – 2011):

- SVR rates increase over time but 30–50% of patients do not achieve SVR

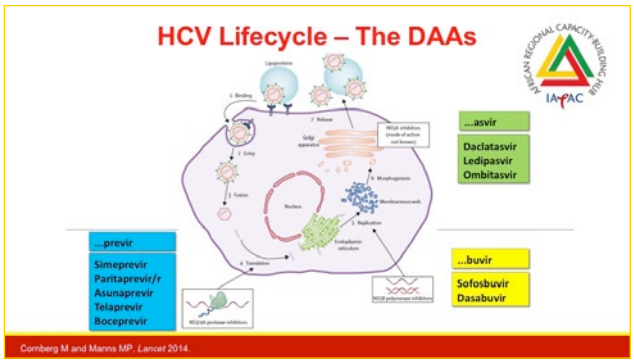
1. Manno M, et al. Lancet 2001; 358: 958; 2. Fried M, et al. N Engl J Med 2002; 347: 975;
3. Hadziyannis S, et al. Ann Intern Med 2004; 140: 346; 4. Zeuzem S, et al. J Hepatol 2005; 43: 250

HCV Lifecycle – DAA Targets



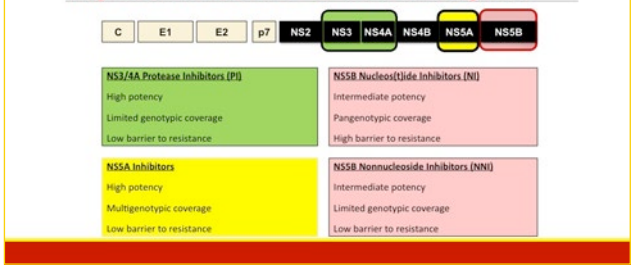
Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

HCV Lifecycle – The DAAs



Cornberg M and Manns MP, *Lancet* 2014.

Key Characteristics of the DAA Agents



DAAs in 2015/2016

Protease Inhibitors	Polymerase inhibitors		NS5A inhibitors
	Nucleotide	Non-nucleoside	
Telaprevir/ Boceprevir	Sofosbuvir	Dasabuvir	Daclatasvir
Simeprevir			Ledipasvir
Paritaprevir/ Ritonavir			Ombitasvir
Asunaprevir			Elbasvir
Grazoprevir			GS5816

The Treatment Landscape in 2015

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

Treatment prioritization needs to be applied in resource-limited settings

Treatment priority	Patient group
Treatment should be prioritized	. Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis . Patients with HIV coinfection . Patients with HBV coinfection . Patients with an indication for liver transplantation . Patients with HCV recurrence after liver transplantation . Patients with clinically significant extra-hepatic manifestations . Patients with debilitating fatigue . Individuals at risk of transmitting HCV
Treatment is justified	. Patients with moderate fibrosis (F2)
Treatment can be deferred	. Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	. Patients with limited life expectancy due to non-liver related comorbidities

Adapted from EASL Treatment Recommendations HCV, April 2015

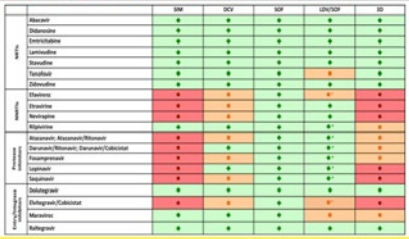
Treatment with Intent to Prevent Transmission to Others

- 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

3D	Sofosbuvir	SOF/LDV	Ribavirin
• Rash • Pruritis • Photosensitivity • Unconjugated hyperbilirubinemia • Fatigue	• Fatigue • Nausea • Headache	• Fatigue	• Hemolytic anaemia • Rash • Insomnia • Asthenia • Teratogenic

Drug-Drug Interactions with ARVs



Immediate Future HCV Treatment Landscape

MODULE 4

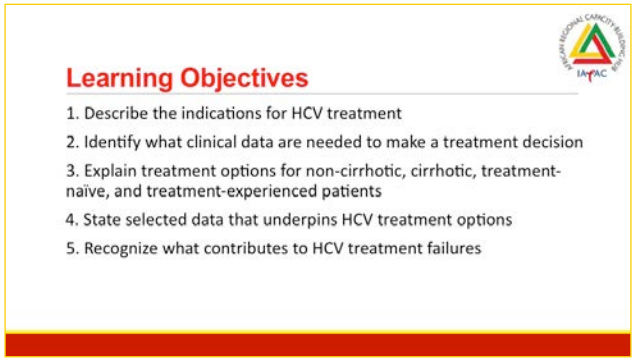
CHRONIC HCV TREATMENT

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

Treatment priority	Patient group
Treatment should be prioritized	. Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis . Patients with HIV coinfection . Patients with HBV coinfection . Patients with an indication for liver transplantation . Patients with HCV recurrence after liver transplantation . Patients with clinically significant extra-hepatic manifestations . Patients with debilitating fatigue . Individuals at risk of transmitting HCV
Treatment is justified	. Patients with moderate fibrosis (F2)
Treatment can be deferred	. Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	. Patients with limited life expectancy due to non-liver related comorbidities

Adapted from EASL Treatment Recommendations HCV. April 2015

Important Data in Choosing a Regimen

HCV treatment history
- Peg-Interferon and ribavirin regimen?
- Previous Protease Inhibitor?

Fibrosis stage?
- Options for fibrosis assessment

- If cirrhosis, is it decompensated?

http://www.hcvguidelines.org

Non-Cirrhotic

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

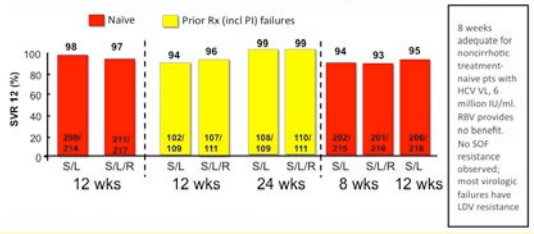
Regimen	HCV Genotype			
	1a	1b	4	5
LDV/SOF	8-12 wks,* no RBV		12 wks, no RBV	12 wks, no RBV
OBV/PTV/RTV + DSV	12 wks + RBV	12 wks, no RBV	Not recommended	Not recommended
OBV/PTV/RTV	Not recommended		12 wks + RBV	Not recommended
SOF + SMV	12 wks, no RBV		12 wks, no RBV	Not recommended
SOF + DCV	12 wks, no RBV		12 wks, no RBV	12 wks, no RBV

DCV, daclatasvir; DSV, dasabuvir; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir;
*Recommendations the same for HCV-monoinfected and HCV/HIV-coinfected patients.
†8 wks may be used in treatment-naïve patients without cirrhosis if baseline HCV RNA <6 million IU/mL, but should be done with caution, especially in patients with F3 fibrosis.

ciation for the Study of Liver Disease Hepatitis C Treatment Guidelines. April 2015.

ION 1, 2, and 3

Sofosbuvir/Ledipasvir ± RBV in Treatment-Naïve and -Experienced GT 1 Patients

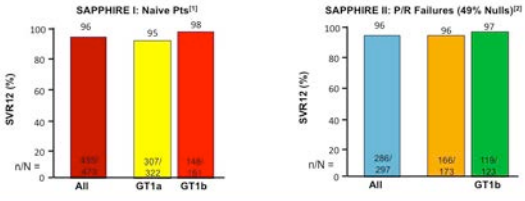


8 weeks adequate for noncirrhotic treatment-naive pts with HCV VL, 6 million IU/mL. RBV provides no benefit. No SOF resistance observed; most virologic failures have LDV resistance

1. Afdhal N, et al. N Engl J Med. 2014;370:1889-1898. 2. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493. 3. Kowdley KV, et al. N Engl J Med. 2014;370:1879-1888.

SAPPHIRE I & II

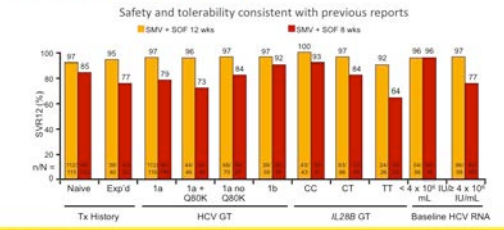
PTV/RTV/OBV + DSV + RBV for 12 Weeks in Non-Cirrhotic Patients



1. Feld J, et al. N Engl J Med. 2014;370:1594-1603. 2. Zeuzem S, et al. N Engl J Med. 2014;370:1604-1614.

OPTIMIST-1

SVR by Patient Subgroup



Kwo P, et al. EASL 2015.

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

SVR12, % (n/N)	Genotype 4	Genotype 5
All	93 (41/44)	95 (39/41)
Treatment-naive	96 (21/22)	95 (20/21)
Treatment-experienced	91 (20/22)	95 (19/20)
Non-cirrhotic	91 (31/34)	97 (31/32)
Cirrhotic	100 (10/10)	89 (8/9)

Abergel A, et al. EASL 2015. Abstract O056.

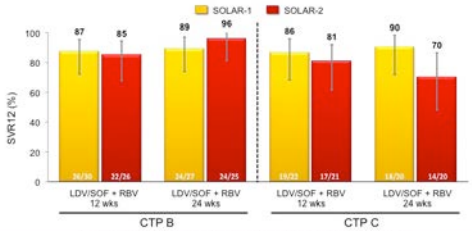
Compensated Cirrhosis

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

Regimen	HCV Genotype 1a	1b	4	5 or 6
LDV/SOF	12 wks + RBV or 24 wks, no RBV or 24 wks + RBV if negative predictors		12 wks + RBV or 24 wks, no RBV or 24 wks + RBV if negative predictors	12 wks + RBV or 24 wks, no RBV or 24 wks + RBV if negative predictors
OBV/PTV/RTV + DSV	24 wks + RBV	12 wks + RBV	Not recommended	Not recommended
OBV/PTV/RTV	Not recommended		24 wks + RBV	Not recommended
SOF + SMV	12 wks + RBV or 24 wks, no RBV		12 wks + RBV or 24 wks, no RBV	Not recommended
SOF + DCV	12 wks + RBV or 24 wks, no RBV		12 wks + RBV or 24 wks, no RBV	12 wks + RBV or 24 wks, no RBV

DCV, daclatasvir; DSV, dasabuvir; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir;
*Recommendations the same for HCV-monoinfected and HCV/HIV-coinfected patients.

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



Comparable efficacy between SOLAR-1 and SOLAR-2 studies

FLAMM, AASLD, 2014, ORAL #239; MANNS, EASL, 2015, GO2

Treatment-Naïve or Peg-IFN/ Ribavirin-Experienced GT 2 or 3

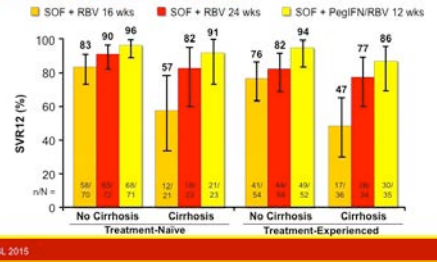
Regimen	No Cirrhosis		Compensated Cirrhosis (Child-Pugh A)	
	GT2	GT3	GT2	GT3
SOF + RBV†	12 wks	24 wks	16-20 wks	Not recommended
SOF + DCV	12 wks, no RBV	12 wks, no RBV	12 wks, no RBV	24 wks + RBV

DCV, daclatasvir; RBV, ribavirin; SOF, sofosbuvir
*Recommendations the same for HCV-monoinfected and HCV/HIV-coinfected pts.
†Best first-line option for genotype 2 HCV; other options may be useful in patients with GT 2 HCV who experience Rx failure on sofosbuvir plus ribavirin.
Suboptimal for genotype 3 HCV, particularly in patients with cirrhosis and previous failure of Peg-IFN/Ribavirin

Adapted from EASL Treatment Guidelines, April 2015.

BOSON Study

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



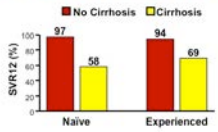
Foster GR, et al. EASL 2015

Daclastavir + Sofosbuvir in Treatment-Naïve and -Experienced GT 3 HCV

ALLY-3[1] study

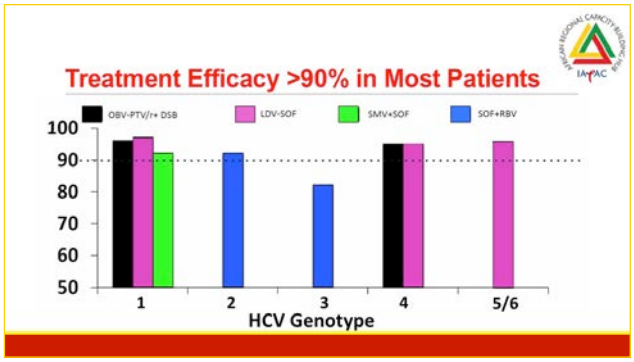
Patients:
- Treatment-naïve and -experienced
  - Prior sofosbuvir included
  - Prior NS5A inhibitors excluded
- Cirrhosis: 21%
- 2 open-label cohorts
- Phase III

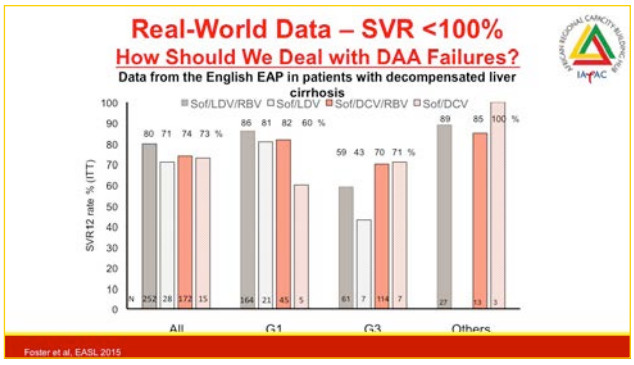
Regimen:
- Daclatasvir + sofosbuvir once daily for 12 wwkes

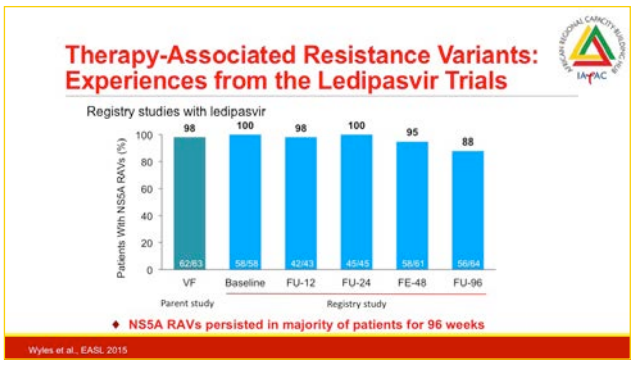


EASL recommendations for DCV + SOF in GT3[2]
- No cirrhosis: DCV + SOF for 12 weeks
- Compensated cirrhosis: DCV + SOF + RBV for 24 weeks

1. Nelson DR, et al. Hepatology. 2015;61:1127-1135. 2. EASL HCV Guidelines. April 2015.


Treatment Efficacy >90% in Most Patients
OBV-PTV/r+ DSB
LDV-SOF
SMV+SOF
SOF+RBV
100
90
80
70
60
50
1
2
3
4
5/6
HCV Genotype

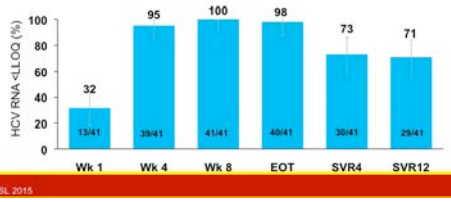

Real-World Data – SVR <100%
How Should We Deal with DAA Failures?
Data from the English EAP in patients with decompensated liver cirrhosis
Sof/LDV/RBV
Sof/LDV
Sof/DCV/RBV
Sof/DCV
SVR12 rate % (ITT)
All
G1
G3
Others
Foster et al, EASL 2015


Therapy-Associated Resistance Variants: Experiences from the Ledipasvir Trials
Registry studies with ledipasvir
Patients With NS5A RAVs (%)
VF
Baseline
FU-12
FU-24
FE-48
FU-96
Parent study
Registry study
NS5A RAVs persisted in majority of patients for 96 weeks
Wyles et al., EASL 2015

Retreatment of SOF/LDV Failures with 24 Weeks of SOF/LDV

24 wks. SOF/LDV after virological failure to SOF/LDV +/- RBV

n=41, cirrhosis n=19, failure to 8 (n=30) or 12 weeks (n=11)
SOF/LDV +/-RBV



Lawitz et al., EASL 2015

Retreatment after DAA Failure

Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Sofosbuvir and daclatasvir or Sofosbuvir and ledipasvir	Genotype 1	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 2 or 3	No	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 4	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Genotype 1	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir and ombitasvir	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis

EASL Treatment Recommendations HCV, April 2015

MODULE 5

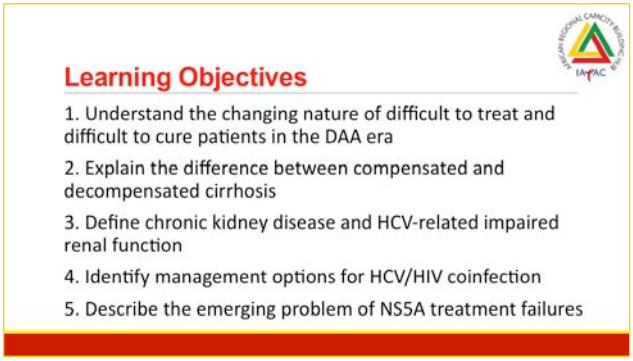
HCV MANAGEMENT IN SPECIFIC POPULATIONS

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

	PAST PEG-IFN/RIBAVIRIN ERA	PRESENT DAA ALL ORAL ERA
DIFFICULT TO CURE	Cirrhosis Genotype 1 High viral load IL28B TT Treatment experienced HIV Post transplant	Advanced/decompensated cirrhosis Genotype 3, advanced fibrosis/ cirrhosis DAA failure
DIFFICULT TO TREAT	Elderly Decompensated cirrhosis Autoimmune disease IFN or Ribavirin intolerant	Chronic kidney disease/ESKD Potential Drug-Drug Interactions Ribavirin intolerant
DIFFICULT TO ACCESS		No access to new DAA therapies

Special Populations

- Compensated and decompensated cirrhosis
- Impaired renal function
- HCV/HIV coinfection
- 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

AASLD/IDSA. HCV Management. http://www.hcvguidelines.org.

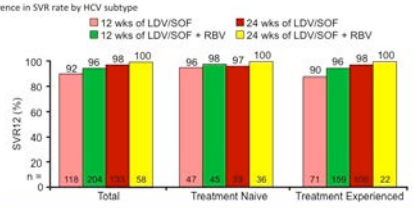
Compensated Cirrhosis

- 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

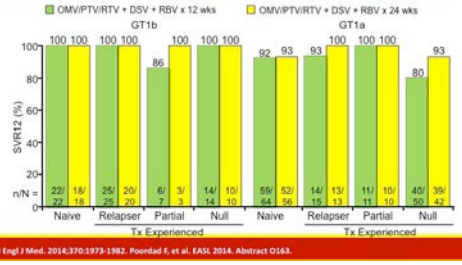
Pooled data (ONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, SIRIUS)

No difference in SVR rate by HCV subtype



Reddy KR, et al. Hepatology. 2015;62:79-86.

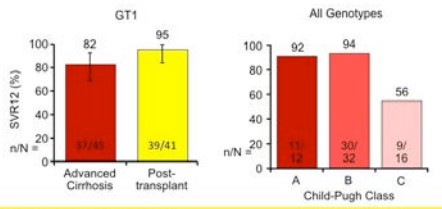
Effect of Treatment Duration with OMV/PTV/RTV + DSV in GT-1 Cirrhosis



Poordad F, et al. N Engl J Med. 2014;370:1973-1982. Poordad F, et al. EASL 2014. Abstract O163.

Daclatasvir and Sofosbuvir ± Ribavirin in GT1

Treatment naive or treatment experienced



Poordad F, et al. EASL 2015. Abstract LO8. ALLY-1 study

Decompensated Cirrhosis: AASLD/IDSA Recommendations

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

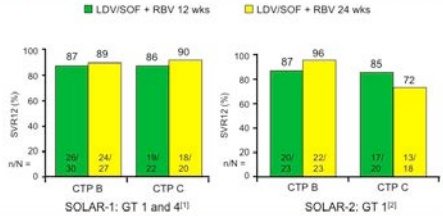
Avoid IFN, TVR, BOC, SMV, OMV/PTV/RTV + DSV, or monotherapy with RBV or DAA

Population	RBV Eligible		RBV Ineligible
	DCV + SOF	LDV/SOF	DCV + SOF
GT1/4	12 wks + low-dose RBV*	12 wks + low-dose RBV*	24 wks
GT1/4, SOF failure	Not recommended	24 wks + low-dose RBV*	Not recommended

*Initial dose of 600 mg/day, increased as tolerated.

AASLD/IDSA. HCV guidelines.

Decompensated Cirrhosis: GT 1 and 4 Trial Data



1. Flamm SL, et al. AASLD 2014. Abstract 239. 2. Manns M, et al. EASL 2015. Abstract G02.

Hepatitis and Renal Disease

- **HCV infection can cause renal disease or be associated with renal disease**
  - Mixed cryoglobulinemia
  - Membranoproliferative glomerulonephritis (MPGN)
  - Polyarteritis nodosa
- **Possibly HCV associated**
  - Focal segmental glomerulosclerosis
  - Proliferative or Membranous 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**

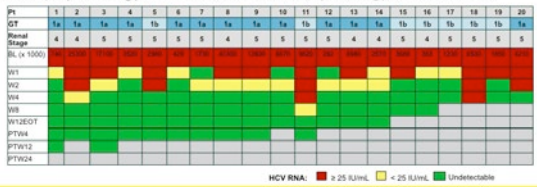
1. Ozkok A, et al. World J Gastroenterol. 2014;20:7544-7554. 2. Saadoun D, et al. Arthritis Care Res (Hoboken). 2011;63:427-435. 3. Satapathy SK, et al. J Clin Exp Hepatol. 2014;4:8-13.

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

Interim analysis of multicenter, open-label phase IIIb study in patients with eGFR <30 mL/min (N = 20)

GT1a: OBV/PTV/RTV + DSV + RBV 200 mg daily for 12 weeks and **GT1b:** OBV/PTV/RTV + DSV for 12 weeks

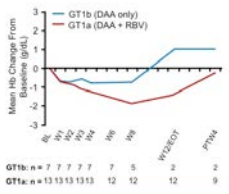
SVR4: 10/10 pts reaching post-treatment week 4 - SVR12: 2/2 pts reaching post-treatment week 12



Pockros PJ, et al. EASL 2015. Abstract L01 – RUBY-1 study

Hematologic Effect of RBV and Overall Safety

- RBV dose interruption in 8/13 GT1a pts (6 in first 4 weeks)
- No Rx-related serious side effects, discontinuations, or significant changes in liver or renal function to date
  - 2 reported serious AEs not attributable to study treatment
- Most AEs mild to moderate



AEs Occurring in > 3 Pts, n	GT1a: OBV/ PTV/RTV + DSV + RBV (n = 13)	GT1b: OBV/ PTV/ RTV + DSV (n = 7)
Anemia	8	0
Fatigue	4	2
Diarrhea	4	1
Nausea	5	0

Pockros PJ, et al. EASL 2015. Abstract L01.

Dosing Recommendations in Renal Impairment

- **OBV/PTV/RTV + DSV**: No dose adjustment required with mild, moderate, or severe renal impairment (CrCl ≥ 15 mL/min)
- **LDV/SOF and SMV + SOF**: No dose adjustment required with mild or moderate renal impairment (CrCl≥30mL/min)
  - Safety and efficacy not established in severe renal impairment or hemodialysis
- **DCV**: No dose adjustment required with any degree of renal impairment (CrCl: ≥15 mL/min)
- **RBV**: Dose adjustment required for CrCl <50 mL/min

CrCl	RBV Dose
30-50 mL/min	Alternating 200 mg and 400 mg every other day
< 30 mL/min	200 mg/day
Hemodialysis	200 mg/day

AASLD/IDSA. HCV guidelines.

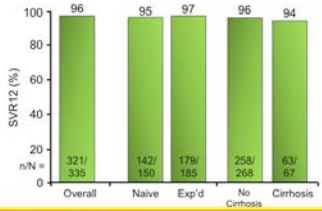
HCV/HIV Coinfection

- No longer considered difficult to cure
- Same recommendations as in HCV mono-infected patients
- Consider drug–drug interactions
  - Avoid combination of LDV and tenofovir if CrCl < 60 mL/min or if receiving tenofovir with RTV-boosted PIs
  - When LDV/SOF and tenofovir are co-administered with ART - monitor for nephrotoxicity
  - Adjust/withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
  - Adjust DCV with atazanavir/RTV, efavirenz, or etravirine
- DCV + SOF ± RBV is recommended when ART regimen changes cannot be made to accommodate other DAAs

AASLD/IDSA. HCV guidelines.

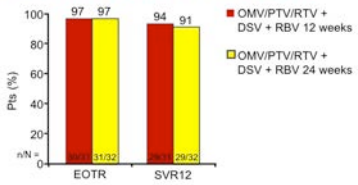
LDV/SOF for 12 Weeks in HCV/HIV Coinfection

GT1 or 4 HCV, 20% with compensated cirrhosis, 55% treatment experienced



Naggie S, et al. CROI 2015. Abstract 152LB – ION-4 study

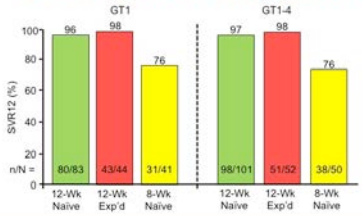
OMV/PTV/RTV + DSV + RBV for 12 vs 24 Weeks in GT1 HCV/HIV Coinfection



65% HCV treatment-naïve patients in 12-week arm, 69% in 24-week arm
19% patients with METAVIR F4 fibrosis

Sulkowski M, et al. JAMA. 2015;313:1223-1231

SOF + DCV in HCV/HIV Coinfection



Wyles DL, et al. NEJM 2015;373:714-25.

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 RAVs that confer decreased susceptibility to NS3 PIs, NS5As recommended
  - If both NS5A and NS3 RAVs detected, treatment within clinical trial recommended

Previous Treatment, Cirrhosis Status	DCV + SOF	LDV/SOF	OMV/PTV/RTV + DSV	SMV + SOF
NS5A, cirrhosis or urgent treatment required	Not recommended	If no NS5A RAVs 24 wks + RBV	Not recommended	If NS5A RAVs but no NS3 RAVs 24 wks + RBV

AASLD/IDSA. HCV guidelines.

LEARNING ACTIVITIES

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:

		Ref. range
Sodium	141 mmol/l	135 — 147
Potassium	4.6 mmol/l	3.3 — 5.3
Creatinine	89 µmol/l	64 — 104
Bilirubin total	13 µmol/l	0 — 21
Bilirubin conjugated	4 µmol/l	0 — 6
Albumin	36g/l	35 — 52
Alkaline phosphatase	62 U/l	40 — 120
γ—Glutamyl Transferase (GGT)	75 U/l	0 — 60

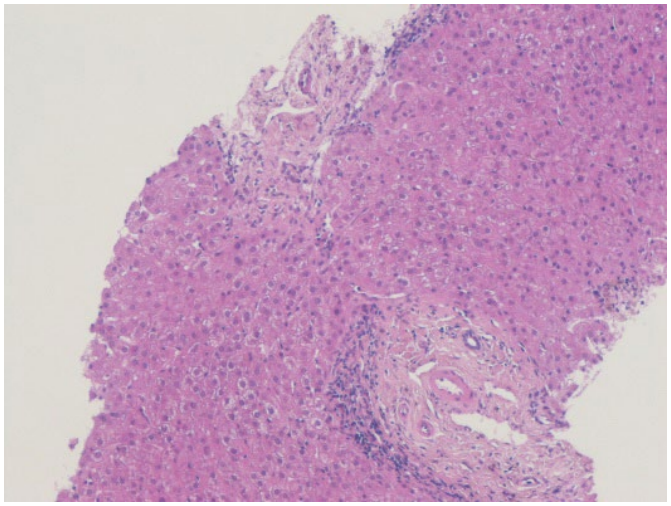
		Ref. range
Alanine transaminase (ALT)	98 U/l	5 — 40
Aspartate transaminase (AST)	60 U/l	5 — 40
White cell count	4.60 x 10^9/l	4 — 10
Hemoglobin	14.3 g/dl	13 — 17
MCV	97.6 fl	79 — 99
Platelets	131 x 10^9/l	137 — 373
Int. normalized ratio (INR)	1.19	

Further workup demonstrated the following:

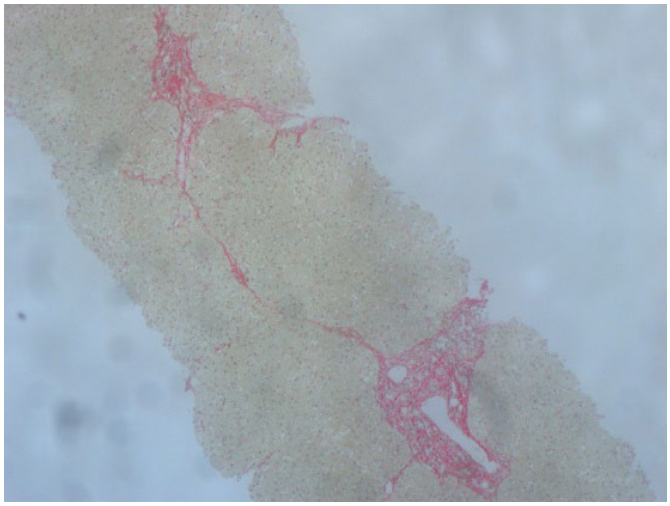
Hep A IgM/IgG – **negative**
Hepatitis B surface antigen – **negative**
Hepatitis B core IgG – **positive**
Hepatitis B surface antibodies **<10 IU/ml**
Hepatitis C antibody – **positive**
HIV Ag/Ab combination assay – **non-reactive**
Hepatitis C PCR – **positive**
Hepatitis C viral load – **7470000 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/mm^3. 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 raltegrevir. 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:

		Ref. range
Sodium	138 mmol/l	135 — 147
Potassium	4.9 mmol/l	3.3 — 5.3
Creatinine	138 µmol/l	64 — 104
Bilirubin total	21 µmol/l	0 — 21
Bilirubin conjugated	7 µmol/l	0 — 6
Albumin	37 g/l	35 — 52
Alkaline phosphatase	115 U/l	40 — 120
γ—Glutamyl Transferase (GGT)	96 U/l	0 — 60
Alanine transaminase (ALT)	115 U/l	5 — 40
Aspartate transaminase (AST)	118 U/l	5 — 40
White cell count	6.8 x 10^9/l	4 — 10
Hemoglobin	13.8 g/dl	13 — 17
MCV	100.6 fl	79 — 99
Platelets	256 x 10^9/l	137 — 373
Int. normalized ratio (INR)	1.08	

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).

NOTES

NOTES

NOTES

IAPAC
INTERNATIONAL ASSOCIATION
OF PROVIDERS OF AIDS CARE

WWW.IAPAC.ORG

IASL
International Association
for the Study of the Liver

WWW.IASLGLOBAL.ORG