

Training workshop on screening, diagnosis and treatment of hepatitis B and C

Session 16

Treatment of HCV infection in special situations

Learning objectives

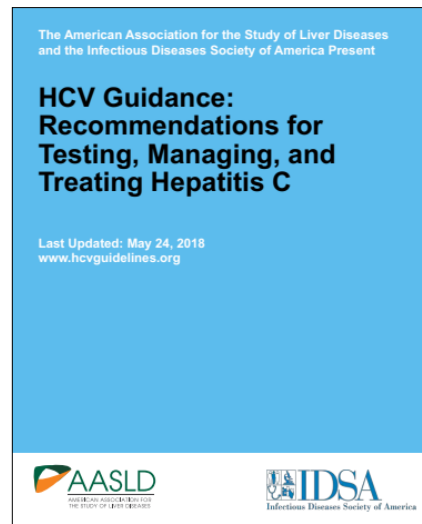
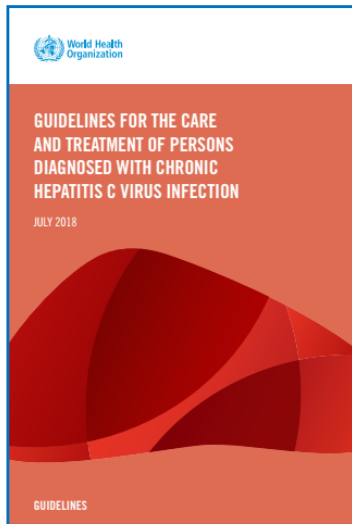
At the end of this sessions, participants would:

- understand the issues that influence management of HCV infection in special patient groups;
- be able to identify the appropriate treatment strategies for individual patients in these special groups.



After this session, we would be able to identify the issues in the management of special populations, evaluate them, choose the appropriate treatment regimen and follow them

Guidelines



- This session is based on two guidelines.
- These are the WHO HCV guidelines and HCV recommendations.

HCV infection in pregnant women

- WHO does not recommend *routine* testing of women for HCV infection.
 - In settings with a $\geq 2\%$ or $\geq 5\%$ HCV antibody seroprevalence, all adults should have access to and be offered HCV serological testing (including pregnant women).
 - Intimate partners of PWID should be offered testing.
- DAAs are not recommended during pregnancy.
- Pregnant women should be offered HCV treatment after breastfeeding has been completed.
- Interferon-based therapy is contraindicated during pregnancy.

GUIDELINES FOR THE CARE AND TREATMENT OF PERSONS DIAGNOSED WITH CHRONIC HEPATITIS C VIRUS INFECTION xvii



Routine screening of pregnant women for anti-HCV is not recommended. One of the major reasons for this is that direct acting antiviral (DAA) drugs are not approved for use in pregnancy.

A pregnant woman, if found to be HCV viraemic infected (confirmed HCV infected), should continue her pregnancy. Breast feeding is recommended as part of infant feeding choices. There is no evidence of HCV mother-to-child transmission from breastfeeding.

Caesarean section is not recommended based on the HCV infection status itself. Options for delivery should be discussed with the doctor.

HCV infection in pregnancy is NOT an indication for termination of pregnancy.

Pregnant women should have assessment of her HCV infection status and liver disease assessment as part of care for her own health.

Women should be offered HCV treatment after breastfeeding is completed.

HCV-exposed infants (babies born to HCV-positive mothers) will need anti-HCV testing at 12–18 months of age.

Overall, more than 90% of HCV-exposed infant will have spontaneously cleared the virus by 12-18 months of age.

Case study: HCV in pregnant women

- 28-year-old woman, asymptomatic, 24 weeks of gestation
 - Routine antenatal visit
 - No significant past history
 - No alcohol, tobacco and substance abuse
 - Examination: unremarkable
 - Investigations

Pregnancy test	Positive
HBsAg	Negative
Anti-HCV	Positive
Anti-HIV	Negative

What tests would you order?

A 28 years old pregnant women was found to be anti-HCV positive in her third trimester.

How to approach this lady?

Case study: HCV in a pregnant woman: laboratory results

Investigations	Values
Haemoglobin (g/dL)	9.8
Platelets ($\times 10^9/\mu\text{L}$)	188
Total bilirubin (mg/dL)	1.2
Albumin (g/dL)	4.0
AST (IU/L)	58 (normal <30)
Prothrombin time (INR)	1.4
HCV RNA quantitative (\log_{10} IU/mL)	6.3
Ultrasound	Liver normal size, echotexture Portal vein diameter 10 mm Spleen normal, no ascites Single live fetus

Laboratory evaluation revealed elevated ALT HCV RNA. USG abdomen showed no evidence of cirrhosis.

What next?

Case study: HCV in a pregnant woman

- What are the issues?
- Hint
 - those for any HCV infection
 - those specific to pregnancy

We need to identify the issues that are related HCV infection in a background of pregnancy.

Case study: HCV in pregnancy: issues

- What is the stage of liver disease?
Cirrhosis versus no cirrhosis
- Is treatment indicated?
- What should be the treatment regimen?
- When to start anti-HCV treatment?
- What is the risk of transmission to the fetus?
- How can transmission be prevented?
- Should she breastfeed the baby?
- Will she require follow up after achieving SVR 12?

These are the issues in an anti-HCV-positive pregnant woman.

HCV in pregnancy: issues

- What is the stage of liver disease?
 $APRI = [58/30] \times 100/188 = \sim 1.0$
 $APRI < 2.0 \rightarrow$ No liver cirrhosis
- Is treatment indicated?
HCV RNA is detectable. Hence, yes.
- When and how should she be treated?

She does not have cirrhosis.

RNA is detectable hence anti-HCV treatment will be needed.

When could we start anti-HCV treatment?

HCV in pregnancy: issues

- What is the stage of liver disease?

$$\text{APRI} = [58/30] \times 100/188 = \sim 1.0$$

APRI < 2.0 → No liver cirrhosis

- Is treatment indicated?

HCV RNA is detectable. Hence, yes.

- When and how should she be treated?

- Currently, DAAs are not recommended during pregnancy.
- Treat after breastfeeding has been completed
- Give any of the pangenotypic regimens for the specified duration.
- No additional follow up is needed after SVR 12 is achieved.



Because DAAs are not approved for use in pregnant women and lactating mothers, she can be treated with a pangenotypic regimen after breastfeeding is completed. In the absence of cirrhosis, she will not need any follow up after achieving SVR 12.

HCV in pregnancy: other important issues

- Offer spouse/partner testing?
- Delivery: as guided by obstetric considerations
- Breastfeeding is safe
- Follow up of the baby for HCV after delivery
 - Do not test soon after birth or in infancy.
 - An antibody test is not helpful.
 - Test at or after 18 months.
 - No urgency to test: HCV progresses slowly and no drugs are available for children <12 years of age.



There are a few additional issues that must be communicated.

First, spouse testing should be considered. Spouse testing is considered because of the ease and benefit of treatment. The risk of HCV transmission between spouses is very low. Hence, if treatment is not a possibility, spouse screening should not be considered. Before embarking upon spouse testing, the impact of a positive result to the individual, family and social life should be considered. Issues including disclosure of the HCV infection status, counseling and education of the individual and partner, issues of stigma and discrimination (and possible violence) should be discussed.

Another important aspect is the mode of delivery. The literature has clearly shown that the risk of HCV transmission from mother to fetus is not reduced by caesarean section; hence, the decision to perform a caesarean section should be based on obstetric indications.

HCV is not transmitted through breastfeeding or through the oro-ental route. Hence, breastfeeding is recommended as part of infant feeding choices after delivery.

All babies born to an anti-HCV-positive mother should be tested for anti-HCV antibody test at the age of 18 months. Anti-HCV testing should not be done earlier because it may test positive due to transplacental transfer of maternal antibodies. Further, early identification of HCV infection in a newborn will not be useful because most (More than 90%) may clear the virus spontaneously.

There are no DAA drugs approved for very young children yet, but this may change in the future.

HCV and HIV coinfection

- HCV/HIV coinfection also adversely affects the course of disease.
 - ❑ It significantly accelerates progression to cirrhosis.
 - ❑ HCC occurs at a younger age and within a shorter time period.
 - ❑ CD4 recovery is impaired after initiation of ART.
 - ❑ HIV disease progression is more rapid.
(compared with persons with HIV or HCV mono-infection)

GUIDELINES FOR THE CARE AND TREATMENT OF PERSONS DIAGNOSED WITH CHRONIC HEPATITIS C VIRUS INFECTION P37



HCV and HIV adversely affect the natural history of each other. In the presence of HIV infection, the rate of progression to cirrhosis and risk of HCC are increased, though the response to anti-HCV DAAs is not affected.

Similarly, in the presence of HCV infection, the rate of HIV progression is increased and the response to antiretroviral drugs is also subdued.

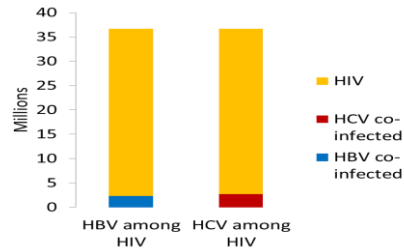
HEPATITIS/HIV COINFECTION

Global:

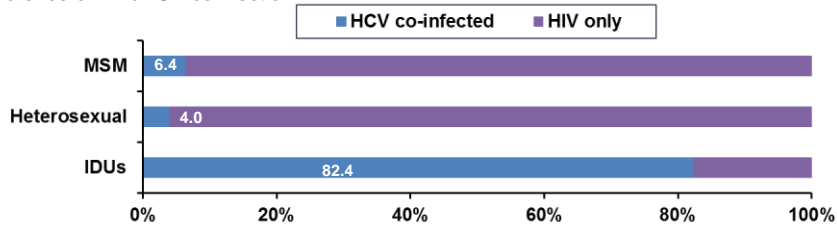
Of the 36.7 million with HIV

– 2.3 million are anti-HCV +

– 2.7 million are HBsAg +



Prevalence of HIV/HCV coinfection



Sources: Easterbrook E, IAS conference, 2015 (HBV); Platt, Lancet Infect Dis, 2016 (HCV), and a slide courtesy of Dr Jürgen Rockstroh



We need to be aware of coinfections. A person can have multiple disease conditions

Typically, there is HIV and hepatitis coinfection, e.g. HIV/HCV (dual infection), HIV/HBV/HCV (triple infection).

In key populations, sexually transmitted infections (STIs) are also issues.

HCV and HIV coinfection

DAA	ABC	ATZr	DRVr	DTG	EFV	LPV/r	NVP	RAL	TDF	TAF	ZDV	XTC
Daclatasvir		Adjust dose			Adjust dose							
Glecaprevir/pibrentasvir												
Sofosbuvir												
Sofosbuvir/ledipasvir		Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF		Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF			Monitor for renal toxicity when used with EFV or boosted protease inhibitor			
Sofosbuvir/velpatasvir		Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF		Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF			Monitor for renal toxicity			

Red = do not co-administer
 Yellow = possible toxicity/interaction/dose adjustment, as specified
 Green = no interaction; can be co-administered

- HCV treatment outcomes with DAAs are comparable in persons with HCV/HIV coinfection to those without HIV.
- There are important drug–drug interactions with pangenotypic DAAs and ART.

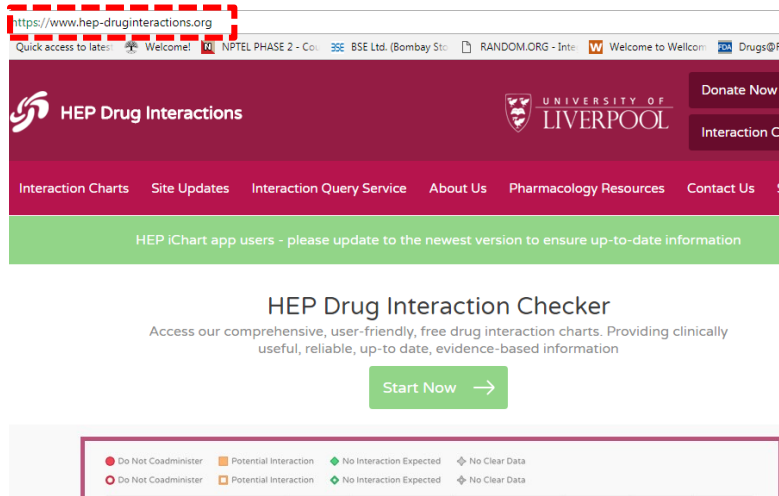
GUIDELINES FOR THE CARE AND TREATMENT OF PERSONS DIAGNOSED WITH CHRONIC HEPATITIS C VIRUS INFECTION P37



In HIV/HCV-coinfected persons, anti-HCV treatment is as effective as in HCV-monoinfected persons. Hence, the dose, duration and outcome of the anti-HCV treatment are not different. But a few of the anti-HCV drugs and ART drugs have significant drug-to-drug interactions.

Before starting HCV treatment in an HIV-positive person, all drug-to-drug interactions should be checked carefully. These interactions, at times, may require a change in ART for the duration of the HCV treatment.

Drug–drug interactions: HCV and HIV drugs



Source: University of Liverpool <https://www.hep-druginteractions.org/>



This is currently the most reliable and most easily accessible source for checking any drug-to-drug interaction of any of the drugs used for HCV treatment.

Please explore this site and recheck from time to time because new information is updated frequently on this site.

Issues in the management of HCV/HIV coinfection

- Concurrent HIV infection modifies HCV disease
 - rapid progression of liver disease
 - more severe disease
 - higher risk of HCC
 - higher mortality rates.
- Treatment regimens are the same as for HIV-negative HCV-monoinfected patients
 - drug choice
 - drug doses (majority)
 - duration of treatment
 - treatment outcome.
- Caution about drug–drug interactions



In an HIV/HCV-coinfected person, anti-HCV treatment is as effective as in an HCV-monoinfected person. Hence, the dose, duration and outcome of the anti-HCV treatment are no different. But a few of the anti-HCV drugs and ART drugs have significant drug-to-drug interactions.

Drug–drug interactions: HCV and HIV drugs

HIV antiviral drugs	Daclatasvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	Simeprevir	Sofosbuvir	Pegylated interferon	Ribavirin
Nucleoside reverse transcriptase inhibitors (NRTIs)								
Abacavir (ABC)	◆	◆	◆	◆	◆	◆	■	■
Emtricitabine (FTC)	◆	◆	◆	◆	◆	◆	■	■
Lamivudine (3TC)	◆	◆	◆	◆	◆	◆	■	■
Tenofovir (TDF)	◆	■	◆	◆	◆	◆	■	■
Zidovudine (AZT)	◆	◆	◆	◆	◆	◆	●	●
HIV entry/integrase inhibitor								
Dolutegravir (DTG)	◆	◆	◆	◆	◆	◆	◆	◆
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)								
Efavirenz (EFV)	■	■	●	●	●	◆	◆	◆
Nevirapine (NVP)	■	◆	●	●	●	◆	◆	◆
Protease inhibitor								
Lopinavir	◆	◆	●	●	●	◆	◆	◆
Ritonavir	■	◆	●	●	●	◆	◆	◆

Source: University of Liverpool hepatitis drug interactions webpage (<http://www.hep-druginteractions.org/>)

- These drugs should not be co-administered
- Potential interaction
- ◆ No clinically significant interaction expected

These are a few of the most commonly encountered drug-to-drug interactions between ART and HCV drugs.

WHO Guidelines

HIV/HCV coinfection

- Persons with HIV/HCV coinfection are at a higher risk for progression of fibrosis and were included in the list of persons prioritized for treatment since the 2014 WHO treatment guidelines. Treatment for HCV infection needs to consider drug–drug interactions with antiretroviral medications.

Because of rapid progression of liver fibrosis in HIV/HCV-coinfected persons, their treatment should be prioritized in resource-constrained settings.

HBV and HCV coinfection

- 3–18% of people who are HBsAg(+) are also HCV infected, and up to 25% of HCV-infected persons are HBV infected.
- Coinfection with HBV/HCV promotes rapid progression of liver disease, and increases the risk of HCC.
- Indications for treatment of HBV infection in patients with HBV/HCV coinfection are the same as those with HBV mono-infection.
- HBV DNA monitoring may be necessary as there is a potential risk of HBV reactivation during DAA treatment.

GUIDELINES FOR THE PREVENTION, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION (WHO 2015) P103

GUIDELINES FOR THE CARE AND TREATMENT OF PERSONS DIAGNOSED WITH CHRONIC HEPATITIS C VIRUS INFECTION P38



It is not uncommon to see HBV and HCV coinfection. This situation is more common among certain high-risk groups such as those with HIV, those who inject drugs, or those on maintenance haemodialysis.

Both HBV and HCV are hepatotropic viruses and cause liver injury. Hence, their coinfection results in relatively rapid progression of liver disease and adverse outcomes.

Issues in the management of HBV/HCV coinfection

- Concurrent HBV infection modifies HCV disease
 - rapid progression of liver disease
 - more severe disease
 - higher risk of HCC
 - **HCV infection may suppress HBV replication.**
- Treatment for HBV/HCV coinfection is the same as for HCV infection
 - drug choice
 - drug doses
 - duration of treatment
 - treatment outcome.
- Assess the need for treatment of HBV infection.
- Be vigilant for HBV reactivation after HCV clearance.



HBV or HCV treatment indications, drugs of choice, duration, etc. are similar to those in monoinfected persons.

In most coinfecting people, HCV is actively replicating while HBV remains dormant. Successful HCV treatment may lead to reactivation of HBV, which can be detected with careful monitoring.

HCV/HBV coinfection: WHO Guidelines

HBV/HCV coinfection

- Persons with HBV/HCV coinfection are at risk for HBV reactivation during and following HCV treatment. An assessment for HBV treatment eligibility with initiation of HBV treatment for those eligible may prevent HBV reactivation during HCV treatment.

The risk of HBV reactivation after HCV treatment is recognized by WHO as well, and we need to actively look for it during follow up after HCV treatment.

HCV in patients with chronic kidney disease (CKD)

- HCV infection is both a cause and a complication of chronic kidney disease, occurring largely in the context of cryoglobulinaemia.
- Type I membranoproliferative glomerulonephritis associated with cryoglobulinaemia is the most common form of kidney disease associated with HCV infection.



HCV infection and chronic kidney disease (CKD) have a mutual interaction with each other. HCV infection increases the risk of CKD. HCV-related CKD may or may not be secondary to cryoglobulinaemia. Similarly, the risk of HCV infection is increased in the presence of CKD. This risk is much more in those on maintenance haemodialysis than those without dialysis.

The risk of HCV infection in the dialysis-dependent population is because of a high risk of HCV transmission due to impaired dialysis hygiene.

HCV infection in CKD: Issues

- Assessment of liver fibrosis

- Ascites and liver stiffness are poor indicators of cirrhosis.
- APRI is not a good indicator of fibrosis.

- Treatment

- Sofosbuvir

- GFR >30 mL/min No dose modification
 - GFR <30 mL/min Not recommended (some people suggest half-dose)*
 - *Problem: sofosbuvir/ledipasvir is a fixed-dose combination



We will understand the important issues in the assessment and management of HCV in a patient with CKD, in particular, those with a glomerular filtration rate (GFR) below 30 mL/min.

Till now, we have learnt that APRI is the most common measure for assessing liver fibrosis but this index does not work in patients with CKD because their serum ALT levels are exceptionally low.

In most of these patients, despite liver disease, especially those on MHD, serum ALT is below the normal limit (<40 IU/L). Falsely low serum ALT results in falsely low APRI, which leads to underestimation of liver fibrosis; further, liver biopsy more risky in such patients because of the risk of bleeding; FibroScan value is also not reliable because of liver congestion secondary to fluid overload.

We also have a problem related to sofosbuvir, which is the backbone in most of the DAA-based anti-HCV treatment regimens. Sofosbuvir is not recommended in those with a GFR below 30 mL/min.

HCV infection in CKD

Chronic kidney disease

- Data are insufficient on the safety and efficacy of sofosbuvir-based regimens in persons with severe renal impairment. Glecaprevir/pibrentasvir is effective against infection with all six major genotypes in persons with chronic kidney disease.

However, these drugs are not available in most parts of the world.



For those with severe renal impairment (GFR below 30 mL/min), glecaprevir/pibrentasvir combination is recommended because these drugs and their metabolites are not excreted in the urine. Unfortunately, access to and affordability of these drugs are limited in several countries.

Issues in HCV management in CKD

- If the GFR >30 mL/min
 - No change in choice of drugs
 - Drug dose
 - Duration of treatment
- If the GFR <30 mL/min
 - DAAAs are not recommended
- Consider treatment with off-label regimens.
- Consider treatment after renal transplantation.

For those with a GFR below 30 mL/min, we need either off-label use of sofosbuvir or plan HCV treatment after renal transplantation.

Treatment of HCV in thalassaemia

- Patients with thalassaemia receive frequent transfusions and have increased frequency of HCV infection.
- The risk has reduced over time with the use of safe blood transfusion practices.
- These patients have low haemoglobin. Hence, avoid ribavirin since it is known to cause haemolysis.
- No change in
 - choice of drugs
 - drug doses
 - duration of treatment.
- Outcomes: comparable to other patients with HCV infection



Patients with thalassaemia are another group of patients who are at a higher risk of acquiring HCV infection because of their frequent need for blood transfusion.

We have keep this in mind while treating HCV infection in such patients. These patients have a low level of haemoglobin. Hence, ribavirin should never be used in such patients because ribavirin causes haemolysis, which could be life-threatening for such patients.

Patients with TB coinfection

- Hepatotoxicity due to anti-TB drugs may pose a problem.
- Hence, first treat for tuberculosis and defer HCV treatment till after that.



In a patient with HCV and TB coinfection we prefer to treat TB first because it is more contagious and may spread to others if left untreated; further, tuberculosis progresses more rapidly than HCV, which takes decades to progress to cirrhosis.

While monitoring an HCV-infected person on ATT for hepatotoxicity we should read the ALT elevation in terms of multiples of the pre-treatment level. In these patients, baseline ALT will be elevated because of HCV infection.

A patient with HCV and TB coinfection, should undergo clinical assessments for the TB as well as HCV disease status.

Treatment of persons with DAA regimen failure

- Treatment of such patients needs special considerations.
- DAA retreatment should be done in specialized centres.

Retreatment after DAA treatment failure

- Currently, only one pangenotypic DAA regimen, sofosbuvir/velpatasvir/voxilaprevir, is approved by a stringent regulatory authority for the retreatment of persons who have previously failed DAA treatment.
- Investigations of a failure to achieve SVR with DAA therapy includes re-examination of adherence and of potential drug–drug interactions.

For those who have failed previous DAA-based anti-HCV treatment, we should seek expert opinion. As of now, only one pangenotypic regimen is approved for retreatment, which is either not available or not affordable in most of the countries.

Summary

- In pregnant women, wait to start treatment till after lactation is over (none of the DAAs is approved for use in pregnancy).
- In persons with HCV/HIV coinfection, drug–drug interactions are a major concern.
- In persons with HCV/HBV coinfection, successful HCV treatment may lead to reactivation of HBV infection.
- In patients with chronic kidney disease and eGFR <30 mL/min, sofosbuvir is currently not approved, and a glecaprevir pibrentasvir combination may be used, if available.
- Ribavirin should be avoided in patients with thalassemia.



In summary, in a pregnant women, HCV treatment should be deferred till breastfeeding is completed.

For HCV/HIV-coinfected people, drug-to-drug interaction is the most important issue.

In HCV/HBV-coinfected people, HCV treatment may lead to HBV reactivation and it should be monitored.

In patients with advanced CKD, a glecaprevir/pibrentasvir combination is preferred.

Ribavirin must be avoided in patients with haemolytic conditions.