

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

Session 14

Natural history of hepatitis C virus infection

Learning objectives

At the end of this session, participants would know the following:

- Difference between anti-HCV positive test and active HCV infection
- Natural history of HCV infection in
 - immunocompetent persons
 - persons with deficient immune function
- Effect of successful treatment on the natural history of HCV.



After this session, participants would be able (i) to differentiate between active HCV and resolved infection; (ii) to understand the natural history of HCV infection in healthy persons as well as in high-risk groups; and (iii) to understand the benefit of virus clearance on HCV-related morbidities and mortality.

WHO Guidelines



This session is based on the HCV guidelines by WHO.
The most recent WHO HCV guidelines was published in 2018.

Acquisition of HCV infection

The usual routes of transmission of HCV infection are:

- **Blood transfusion**
- **Unsafe injection practices**
 - **health care-related**
 - **injection drug use**
- **Nosocomial**
 - unsterile surgical procedures, haemodialysis, tissue transplantation
- **Body piercing, tattooing**
- **Sexual activity**
- **Mother to child**



Hepatitis C virus is acquired through the parenteral route, which are very similar to that of hepatitis B and HIV.

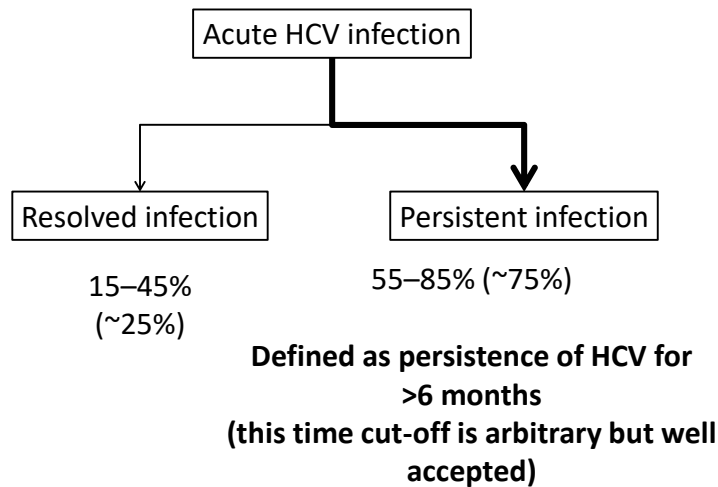
Transfusion of unsafe blood and unsafe injection practices are the most common sources of HCV transmission globally.

In contrast to HBV and HIV, hepatitis C is infrequently transmitted from a pregnant woman to her baby in utero.

Mother- to child transmission is possible however more than 90% of infants born to HCV-infected pregnant women will spontaneously clear by 12-18 months of age.

Further, sexual transmission of HCV, in particular among those who are in heterosexual monogamous relationships, is very infrequent.

Natural history of HCV infection



Following an infection with HCV, 15–45% (approximately one third) resolve and 55–85% (2/3rd) progress to chronic infection.

Persistent infection is defined as persistence of HCV for >6 months. This time cut-off of 6 months is arbitrary and primarily taken as an analogy to chronic hepatitis B.

Acute HCV

- Incubation period: 2 weeks to 6 months
- Variable manifestations
 - asymptomatic
 - mild non-specific symptoms
 - mild clinical jaundice in up to 15% of patients
- Serum aminotransferase (ALT, AST) levels may be high (up to 10 times upper reference limit)
- Usually goes unrecognized
- May be identified in those at high risk and on regular monitoring for HCV infection (e.g. persons on maintenance haemodialysis)



Following HCV exposure in a susceptible host, the virus causes acute HCV infection, which is mostly asymptomatic. The majority of patients with acute HCV are either asymptomatic or have non-specific systemic features such as low-grade fever, anorexia, etc. Clinical jaundice is very uncommon and hence the infection goes unnoticed. In patients with acute HCV, serum ALT and AST levels may rise to 10 times the ULN but the enzyme elevation is lesser than in those with acute viral hepatitis due to A, E or B viruses.

Acute HCV infection

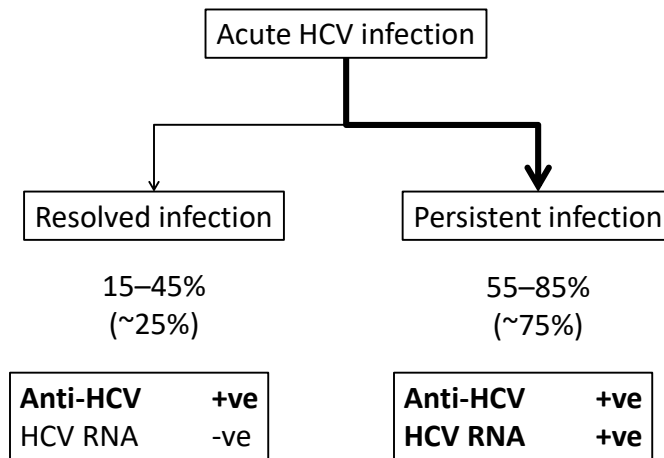
- Diagnosis is difficult
- A person with HCV infection and one of the following:
 - recent change in anti-HCV antibody/HCV RNA status (from -ve to +ve)
 - recent jaundice or ALT >10 x ULN (beginning <20 weeks ago)

Hajarizadeh B, Grebely J, Dore GJ. Case definitions for acute hepatitis C virus infection: a systematic review. J Hepatol. 2012 Dec;57(6):1349-60.



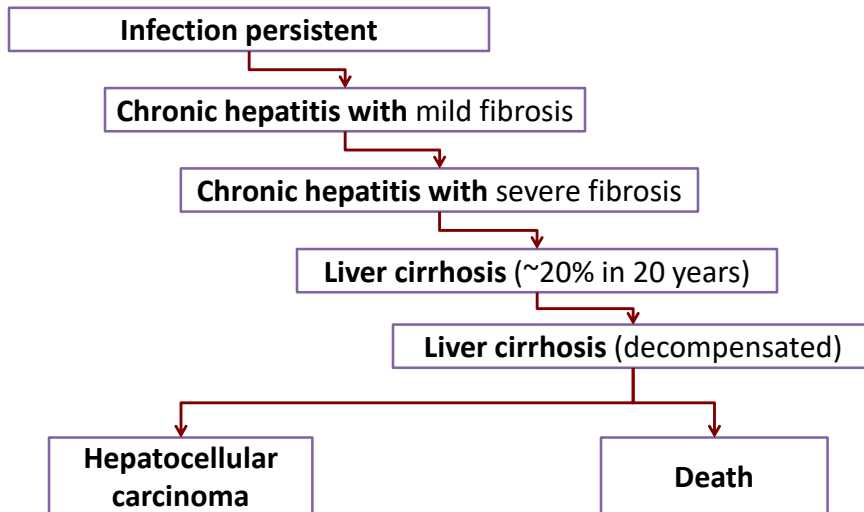
Empirically, acute HCV can be diagnosed in a person only if we find significant ALT elevation coupled with seroconversion from a negative anti-HCV test to a positive anti-HCV test.

Natural history of HCV infection



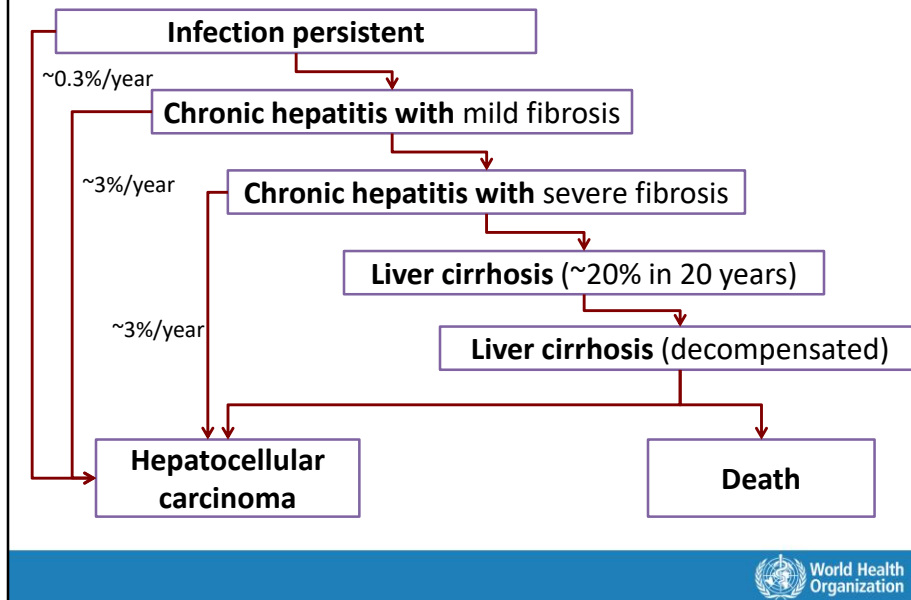
Usually, anti-HCV remains positive for life after the acute stage of the infection. It means that both resolved infection and persistent infection are anti-HCV positive. However, only patients with persistent infection remain HCV RNA positive (viraemia infection). Hence, we can distinguish persistent infection from resolved infection by checking for the presence of HCV RNA.

Natural history of HCV infection



Liver fibrosis is a result of ongoing liver injury and the healing process. Hence, liver fibrosis progresses as a continuum from no fibrosis, mild, moderate and severe fibrosis to frank cirrhosis. The most important key determinant in the natural history of HCV is the presence or absence of cirrhosis because it determines the drug of choice, duration of treatment, risk of relapse following treatment, and need for regular follow up after successful virus eradication.

Natural history of HCV infection



Even though it is rare, patients who have chronic hepatitis develop HCC. Therefore, we should keep in mind that even such patients do have a risk of developing HCC.

Natural history following acute HCV

Treatment-naïve patients

- **Chronic infection**
A person who continues to have detectable HCV RNA in the blood **beyond 6 months** after acute infection
- **Resolved infection**
HCV disappears from the body within 6 months after infection. However, anti-HCV usually continues to be positive.

Treatment-experienced patients

- **Relapse** is rare once RNA is spontaneously cleared.
- **Reinfection** can occur following repeat exposure (e.g. in those who continue to be at high risk: PWID, those on dialysis)



HCV infection is usually identified by the presence of anti-HCV antibody in the blood. It is important to realize that the presence of anti-HCV antibody does not indicate active infection because after natural clearance or successful treatment of HCV infection, the antibody continues to remain positive throughout life. In a treatment-naïve person, the presence of anti-HCV does not indicate chronic infection or the need for treatment but we need to test for HCV RNA (qualitative or quantitative) to identify active or chronic HCV infection.

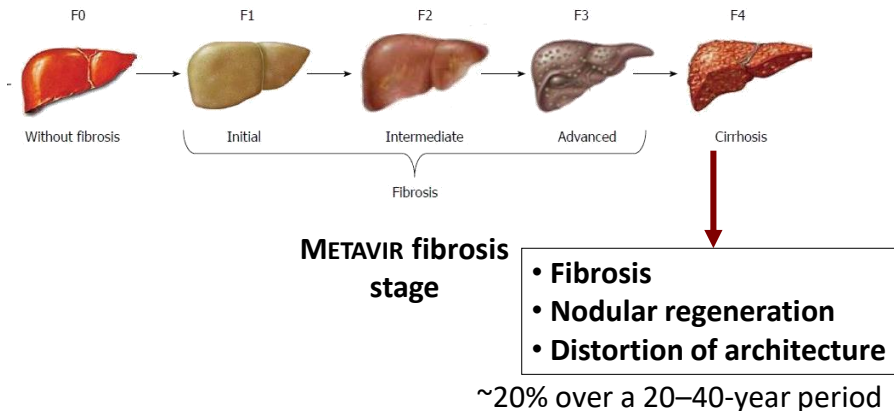
Today, the standard of care for HCV is treatment with orally administered drugs that are highly effective and about 90–95% of those treated successfully clear the virus. However, in a small proportion of treated persons, the virus may come back after some time, which is known as relapse and should be differentiated from reinfection.

If the virus reappears within 12 weeks of stopping treatment, it should be considered as relapse but if the virus reappears after 12 weeks, then it indicates reinfection.

Anti-HCV antibody does not provide immunity against HCV infection. Further, successful HCV treatment does not provide lifelong protection. Hence, akin to any other infection, re-exposure to the virus results in HCV reinfection, which is quite common among certain high-risk groups such as those on maintenance haemodialysis, etc.

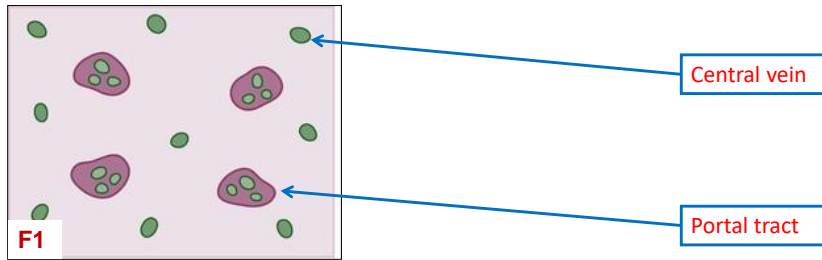
Natural history of chronic hepatitis C

- Chronic infection leads to long-term inflammation.
- This results in fibrosis or scarring.



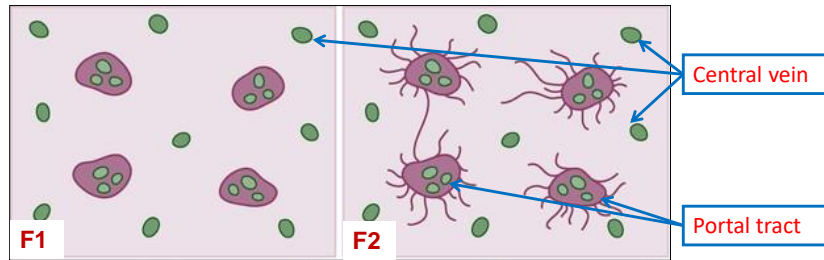
Chronic infection leads to long-term inflammation. It results in fibrosis or scarring. The METAVIR score is a tool used to evaluate the severity of fibrosis seen on a liver biopsy sample from a person who has hepatitis C. The grade indicates the amount of inflammation in the liver and the stage represents the amount of scarring or fibrosis. In this score, F4 means liver cirrhosis, in which there is fibrosis, nodular regeneration and distortion of architecture. The rate is less than 20% in a 20–40-year period.

Prolonged liver injury leads to scarring (fibrosis)



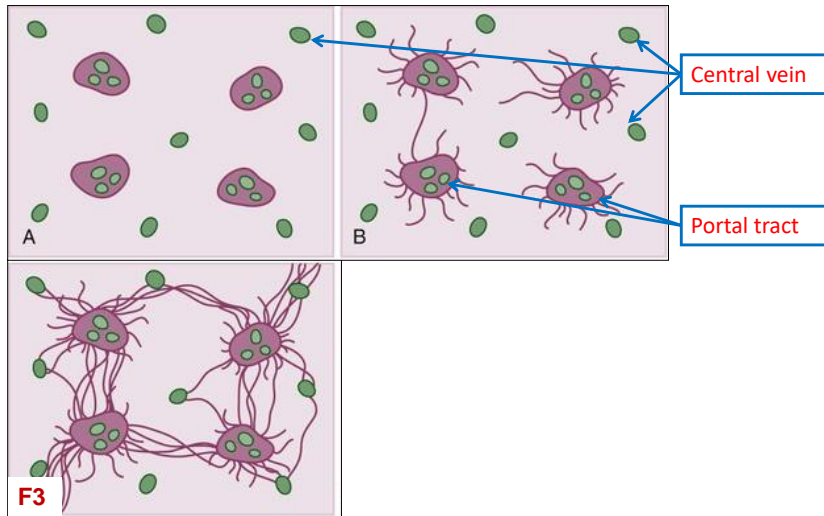
A fibrosis score of F1 (portal fibrosis without septa) means that the portal tracts are showing expansion because of fibrosis but fibrosis has not expanded into the hepatic lobule.

Prolonged liver injury leads to scarring (fibrosis)



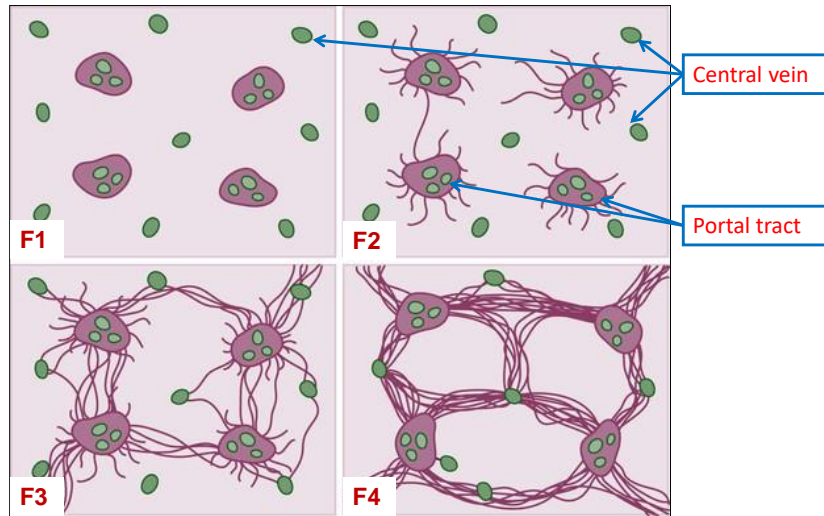
A fibrosis score of F2 (portal fibrosis with few septae) means the fibrosis has started expanding into the hepatic lobules beyond the portal tract, though the lobular fibrosis is limited. Such lobular fibrous septae are few in number, thin, and run from one to another portal tract. At this stage of fibrosis, there are no fibrous septae between the portal tract and central vein.

Prolonged liver injury leads to scarring (fibrosis)



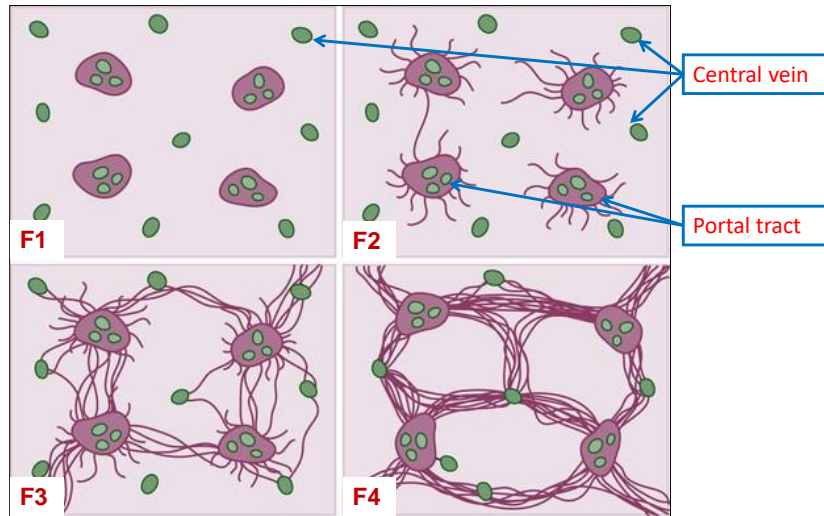
A fibrosis score of F3 (numerous septae without cirrhosis): means that fibrosis has extended well into the hepatic lobular parenchyma. The parenchymal fibrous septae are numerous, thicker and predominantly run between the adjacent portal tracts with a few thin septae running from the portal tracts to the central veins.

Prolonged liver injury leads to scarring (fibrosis)



A fibrosis score of F4 (cirrhosis) means that there is histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury. In this stage, numerous thick septae connect either the portal tracts to the adjacent portal tracts or portal tracts to the central veins.

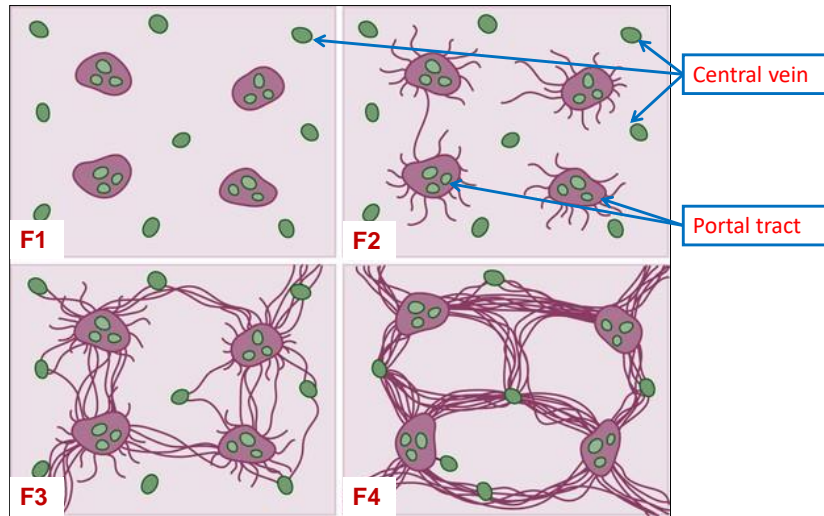
Prolonged liver injury leads to scarring (fibrosis)



Scarring/fibrosis: particularly affects the central vein and portal tracts

In the presence of numerous thick fibrous septae, the entire liver parenchyma is replaced by numerous small nodules of parenchymal cells, which are surrounded by thick fibrous bands.

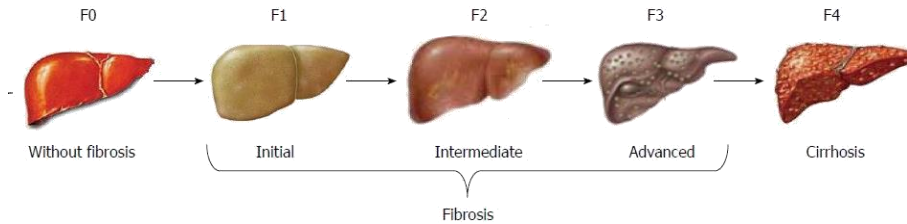
Prolonged liver injury leads to scarring (fibrosis)



Fibrosis affects flow of blood through the portal tracts and hepatic lobules

These septae distort the internal fine architecture of the hepatic lobule and hence the flow of blood across the liver is disturbed and obstructed, which results in portal hypertension and formation of varices.

Progression of liver fibrosis



METAVIR fibrosis stages: F0–F4

Cirrhosis: An advanced stage of liver fibrosis characterized by

- extensive fibrosis
- nodular regeneration
- distortion of liver architecture

= F4 fibrosis



Cirrhosis is an advanced or terminal stage of liver fibrosis characterized by extensive fibrosis, nodular regeneration, and distortion of liver architecture.

HCV: natural history in HIV co-infected person

- Lower rates of spontaneous HCV clearance
- Relatively rapid liver disease progression
- Impaired recovery of CD4 cell count following effective antiretroviral therapy
- Accelerated progression to cirrhosis, decompensation and hepatocellular carcinoma (HCC)
- Higher rates of HCC and at a younger age



HIV infection induces an immunocompromised stage in the host. In a person with HCV/HIV coinfection, both the viruses adversely affect the natural history of each other.

In terms of HCV: the possibility of its natural clearance is reduced, rate of fibrosis progression is increased, the risk of HCC is increased.

In terms of HIV: the recovery of CD4 cell count is impaired after effective antiretroviral therapy if HCV remains untreated.

Hence, HIV/HCV-coinfected patients should be identified and be treated on a priority basis.

Effect of treatment on natural history

Chronic HCV, no cirrhosis

- Halts progression of fibrosis
- Marked reduction in risk of progression to cirrhosis
- Marked reduction in risk of developing HCC
- ? Reversal of fibrosis

Chronic HCV with cirrhosis

- Reduced risk of developing HCC
- Reduced risk of decompensation
- ? Reversal of cirrhosis – in the early stages



Cure of HCV infection has a beneficial impact on the host. The extent and type of benefit varies according to the status of liver disease at the time of treatment.

In a non-cirrhotic person, successful virus eradication reduces the rate of fibrosis progression with a consequent decrease in the risk of cirrhosis and HCC. Early stages of fibrosis may also reverse in due course of time, though we have limited evidences to support this.

In a person if the HCV infection has already progressed to cirrhosis then the benefits are relatively limited. These patients will have a reduced risk of developing HCC and in a fraction of patients, decompensated cirrhosis may reverse to a compensated stage, which has a relatively better prognosis than at the decompensated stage.

Seeing all the above-mentioned benefits, every attempt should be made to identify a patient infected with HCV in a non-cirrhotic stage. Further, everyone with active HCV infection must be treated, regardless of the stage of liver disease.

Summary

- HCV infection can be either acute or persistent.
- Acute HCV infection usually goes unnoticed.
- A proportion of those with HCV infection clear the virus spontaneously.
- Among those with chronic HCV infection, ~20% develop cirrhosis over 20–40 years.
- Among those with cirrhosis due to HCV infection, ~3% develop HCC every year.
- Coexistent HIV infection accelerates the development of cirrhosis.
- Successful anti-HCV treatment reduces the risk of progression to cirrhosis, decompensation, HCC and liver-related death.



The key messages of the presentation are:

- acute HCV is difficult to identify and most of the time goes unnoticed;
- In adults, a small proportion of acute HCV infection resolves spontaneously but the majority progresses to chronic HCV;
- a small proportion of those with chronic HCV develop cirrhosis;
- patients with HCV-related cirrhosis may develop HCC, which is in contrast to HBV, in which patients without cirrhosis can also develop HCC;
- HIV infection accelerates HCV progression and hence HCV/HIV-coinfected people should be treated on a priority basis;
- successful virus clearance reduces HCV-related long term morbidities and mortality.