TRAINING MODULES ON HEPATITIS B AND C SCREENING, DIAGNOSIS AND TREATMENT

World Health Organization

Training Modules on Hepatitis B and C Screening, Diagnosis and Treatment
ISBN: 978-92-9022-747-2

Suggested citation. Training Modules on Hepatitis B and C Screening, Diagnosis and Treatment; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Printed in India

Training Modules on Hepatitis B and C Screening, Diagnosis and Treatment

Contents

Foreword

Viral hepatitis is a major public health threat, with serious consequences such as cirrhosis and liver cancer. Together, the South-east Asia and Western Pacific regions account for two-thirds of the world's deaths attributable to hepatitis B and C. Cirrhosis and liver cancer is within the top ten causes of death in both regions, with countries having some of the highest incidence of new cases of liver cancer globally.

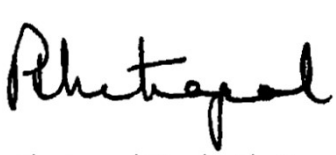
It is without doubt, action must be taken to change this increasing trajectory of advanced liver disease and liver cancer. Earlier testing and treatment can prevent progression of disease and reduce the risk of developing liver cancer. Hepatitis B is manageable with highly effective medicines. Hepatitis C is curable with oral direct acting antiviral medicines which cure more than 95% of people who complete the 2-3 months therapy.

Many countries are developing or accelerating their national responses for comprehensive prevention, treatment and care for viral hepatitis, as part of the call to action towards elimination of viral hepatitis as a public health threat by 2030. At the core of this action, is the delivery of good quality hepatitis care as part of existing health services, which is safe, affordable, accessible and equitable. Healthcare providers must have the training and capacity to deliver this.

The Training Modules on screening, diagnosis and treatment of hepatitis B and C aims to assist this objective; and is based on WHO guidelines. Specifically, the modules help provide the essential knowledge for practice to those at the frontline of public health action on hepatitis, namely physicians, nurses, pharmacists, community health workers and staff providing hepatitis care.

Guidelines for delivering the best practices in hepatitis care evolve and change with time, based on new evidence. This training module has to keep pace with such changes, and for this reason, is being published electronically as a series of individual chapters. This will allow for individual chapters to be reviewed and updated separately in accordance to new evidence and best practice. The modules should be used in conjunction with international and national guidelines. Users are encouraged to supplement the content with existing evidence-based effective practices at their local level and to bring such practices forward for broader consideration and possible incorporation into standard practice at a national level. While these guidelines reflect normal expectations, there will be circumstances that may require professional judgement of the local healthcare provider.

We hope these training modules will be a tool to assist work in countries and healthcare providers.



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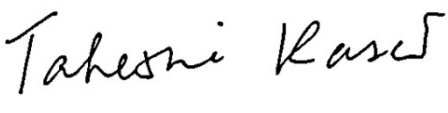
Regional Director for WHO South-East Asia Region



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Introduction

Viral hepatitis is the seventh leading cause of death worldwide. Annual deaths from hepatitis (1.34 million) exceed the number of AIDS-related deaths (1.0 million) and approach the mortality associated with tuberculosis (1.67 million).

Viral hepatitis is caused by different virus types. The most serious are hepatitis B and C viruses, which together cause around 90% of hepatitis deaths worldwide. An estimated 257 million people globally are infected with hepatitis B virus (HBV), and roughly 900 000 per year die of HBV. It is estimated that 71 million people around the world are infected with hepatitis C virus (HCV) and that 400 000 people die of HCV-related causes each year.

The WHO South-East Asia Region (SEAR) is home to an estimated 39 million people with chronic HBV and an estimated 10 million people with HCV. An estimated 410 000 people in the Region die annually due to viral hepatitis, with chronic complications associated with HBV and HCV accounting for 78 % of the total.

The WHO Western Pacific Region (WPR) shoulders a substantial burden with an estimated 115 million people living with hepatitis B and 14 million living hepatitis C. The Region accounts for almost 40% of all global hepatitis related deaths. Liver cancer is the top 6th cause of death in the region, mostly due to chronic hepatitis B and C. Six out of the 10 countries with highest incidence of new liver cancer cases are in WPR.

The increasing trend in hepatitis-related deaths is alarming and action can be taken. Cirrhosis and liver cancer due to hepatitis is preventable as treatment prevents disease progression and hepatitis C infection is curable. The Global Health Sector Strategy (GHSS) for Viral Hepatitis 2016-2021 outlines the vision of elimination of viral hepatitis as a public threat by 2030, as part of Sustainable Development Goals for health.

Many countries are developing their national response for comprehensive prevention, treatment and care for hepatitis, as part of Health for All. Delivery of services for screening, diagnosis and treatment of hepatitis B and C as part of existing health services underlies universal health coverage. Capacity to deliver good quality services by all cadres of health care providers for hepatitis care is important.

These training modules have been developed by WHO South-East Asia and Western Pacific Regional Offices as part of bi-regional collaboration, and were developed following global WHO guidelines for hepatitis which can be adapted to country-specific needs. The modules are available publicly for the use capacity building of health care providers.

We would like to thank the WHO collaborating center for viral hepatitis at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India and the WHO collaborating center for chronic hepatitis and liver cancer, Kanazawa University, Kanazawa, Japan for their technical assistance in the development of these modules. The bi-regional pilot workshops were supported by UNITAID funding through the Coalition PLUS HIV/HCV Drug Affordability Project with TREAT Asia.

Sample: pre-and post-workshop questionnaire, to be adapted as appropriate

Training Workshop on Hepatitis B and Hepatitis C screening, diagnosis and treatment
Instruction: Please circle at the correct answer(s).

Your initial: _____

1. Which of the following statement is NOT correct?
   A. There are five main hepatitis viruses which infect human
   B. HBV and HCV can cause liver cirrhosis and hepatocellular carcinoma
   C. The main routes of transmission of HBV are perinatal and bloodborne
   D. More than 90% of patients with chronic HBV infection can be cured by drug treatment.

2. Which of the following statements is NOT correct?
   A. HCV is transmitted mainly through exposure to contaminated blood products
   B. Persons with acute HCV infection are often asymptomatic.
   C. HCV frequently affects organs other than the liver, such as joints and the kidneys.
   D. HIV/HCV-coinfected patients have faster progression to cirrhosis.

3. Which of the following statements is NOT correct?
   A. A positive HCV antibody test does not confirm the presence of chronic HCV infection
   B. All patients who test positive for HCV antibody should have HCV RNA testing to confirm chronic infection.
   C. The definition of chronic HCV infection is the presence of HCV RNA in the blood over six months after the estimated time of infection.
   D. We can assess the degree of liver fibrosis by testing ALT/AST, albumin, INR and bilirubin.

4. We know the value of AST and Platelet of a patient. By which test can we assess liver fibrosis?
   A. FIB-4
   B. APRI
   C. FibroTest
   D. Fibroscan

5. Which of the following is NOT correct describing acute HBV infection?
   A. It is characterized by the presence of anti-HBs during the acute phase
   B. HBsAg appears firstly after acquisition of HBV infection
   C. IgM anti-HBc appears soon after the appearance of HBsAg
   D. The clinical symptoms, aminotransferases elevation and HBsAg usually disappear within 6 months

6. Which is NOT correct interpreting HBV serological markers?
   A. HBsAg +, Anti-HBs -, Anti-HBc (IgM) +, Anti-HBc (Total) + ; Recent infection
   B. HBsAg +, Anti-HBs-, Anti-HBc (IgM) -, Anti-HBc (Total) + ; Chronic infection
   C. HBsAg -, Anti-HBs+, Anti-HBc (Total) +; Immunity due to vaccination
   D. HBsAg -, Anti-HBs-, Anti-HBc (Total) -; Never infected

7. A patient has Anti-HCV (+) and HCV RNA (-). What is the interpretation?
   A. Recent infection
   B. Chronic infection
   C. Never infected
   D. Infection resolved or cured

8. Which person does NOT have screening for HBV?
   A. A 24 year-old pregnant woman (the HBsAg seroprevalence is 5% in her country)
   B. A 52 year-old man with general malaise and jaundice
   C. A 7 year-old boy his brother is with HBV infection
   D. A 22 year-old woman. She is a nurse and has not been vaccinated previously

9. Which of the following is NOT correct?
   A. WHO recommends tenofovir or entecavir to all adults, adolescents and children aged 12 years or older in whom antiviral therapy for HBV in indicated
   B. Nucleos(t)ide analogues (NAs) with a low barrier to resistance can lead to drug resistance and are not recommended
   C. For the HBV treatment by NAs, lifelong antiviral therapy is generally required
   D. Discontinuation of NAs may be considered in some persons with clinical evidence of cirrhosis

10. Which is NOT correct regarding monitoring during treatment of HBV infection?
   A. ALT, HBsAg, HBeAg and HBV DNA levels should be monitored annually.
   B. Non-invasive tests to assess for the presence of cirrhosis are recommended to be monitored annually
   C. More frequent monitoring is recommended for persons in whom treatment has been discontinuation
   D. In a patient with cirrhosis and family history of HCC, surveillance for liver cancer should be done every 12 months

11. Which of the following is NOT correct?
   A. All HIV/HBV co-infected individuals should receive antiretroviral therapy regardless of CD4 count
   B. HBV/HCV co-infected individuals should usually receive initial treatment for HCV
   C. PWID are at increased risk of acute and chronic hepatitis B and liver related disease, and therefore require additional care
   D. In persons with HIV/HCV co-infection, treatment for HCV infection need to consider drug-drug interaction with anti-retroviral medications.

12. Based on the 2018 WHO hepatitis C treatment guidance, which one of the following should be considered “highest priority” for hepatitis C treatment?
   A. Coinfection with tuberculosis
   B. Coinfection with HIV
   C. People who inject drugs
   D. Type 2 diabetes mellitus

13. Based on the 2018 WHO hepatitis C treatment guidance, which one of the following is pan-genotypic
   regimen for hepatitis C treatment?
   A. Sofosbuvir and ledipasvir
   B. Sofosbuvir and ribavirin
   C. Sofosbuvir and simeprevir
   D. Sofosbuvir and velpatasvir

**********ANSWERS**********

1. Which of the following statement is NOT correct?
Answer: *D*

A. *Correct. There are five hepatitis virus (HAV, HBV, HCV, HDV, HEV) which infect human.*
B. *Correct. HBV and HCV can cause chronic hepatitis consequently related to liver cirrhosis and hepatocellular carcinoma.*
C. *Correct. The main routes of transmission of HBV are perinatal and bloodborne*
D. *Incorrect. More than 90% of patients with chronic HCV infection can be cured by drug treatment (direct-antiviral agents). Patients with chronic HBV infection can be rarely cured.*

2. Which of the following statements is NOT correct?
Answer: C

A. *Correct. HCV is transmitted mainly through exposure to contaminated blood products including blood.*
B. *Correct. Persons with acute HCV infection are often asymptomatic and difficult to diagnose.*
C. *Incorrect. HCV infection can lead to extrahepatic manifestations. Cryoglobulinemia is one of the most common disorders associated with HCV and affects the skin, kidneys, nerves and joints. But the frequency is not high.*
D. *Correct. HIV/HCV-coinfected patients have significantly accelerated progression to cirrhosis and more rapid HIV disease progression.*

3. Which of the following statements is NOT correct?
Answer: *D*

A. *Correct. HCV RNA is necessary to confirm HCV infection.*
B. *Correct. All patients who test positive for HCV antibody should have HCV RNA testing to confirm chronic infection.*
C. *Correct. The definition of chronic HCV infection is the presence of HCV RNA in the blood over six months after the estimated time of infection.*
D. *Incorrect. We can assess the degree of liver fibrosis by non-invasive test, APRI score calculating by AST and platelet.*

4. We know the value of AST and Platelet of a patient. By which test can we assess liver fibrosis?
Answer: *B*

A. *Incorrect. FIB-4 is calculated by age, AST, ALT and platelet*
B. *Correct. APRI is calculated by AST and platelet. Upper limit of normal for AST is necessary for calculation.*
C. *Incorrect. FibroTest is calculated by GGT, haptoglobin, bilirubin, apoprotein A1 and α2-macroglobulin.*
D. *Incorrect. Fibroscan is transient elastography and need dedicated equipment.*

5. Which of the following is NOT correct describing acute HBV infection?
Answer: *A*

A. *Incorrect. The present of anti-HBs during the acute phase means closely to cure or cured. It is characterized by the presence of IgM anti-HBc duing the acute phase.*
B. *Correct. HBsAg is the first marker to appear following HBV infection*
C. *Correct. IgM anti-HBc appears soon after the appearance of HBsAg*
D. *Correct. Acute hepatitis with HBV is usually cured within 6 months.*

6. Which is NOT correct interpreting HBV serological markers?
Answer: *C*

A. Correct.
B. Correct.
C. Incorrect. Immunity due to natural infection and recovery. Anti-HBc (Total)+ indicates resolved infection. In immunity due to vaccination, the pattern of HBV markers is HBsAg, Anti-HBs+, Anti-HBc-.
D. Correct.

7. A patient has Anti-HCV (+) and HCV (-). What is the interpretation?
Answer: *D*

A. Incorrect. Anti-HCV (-) and HCV RNA (+) indicates acute or recent infection.
B. Incorrect. Anti-HCV (+) and HCV RNA (+) indicates chronic infection.
C. Incorrect. Negative for both tests means never infected.
D. Correct. HCV RNA was cleared spontaneously or after treatment

8. Which person does NOT have screening for HBV?
Answer: *D*

A. Correct. Routine screening for HBV in pregnant woman is recommended in the HBsAg seroprevalence more than 2% or 5% setting.
B. Correct. General malaise and jaundice are symptoms with acute hepatitis. Screening for HBV is recommended to patient suspected viral hepatitis.
C. Correct. The infection route of the brother is suspected by mother to child transmission. Screening for HBV is recommended to family members suspected mother to child transmission.
D. Incorrect. HBV vaccination is recommended to health care workers. But, screening for HBV is not recommended before vaccination.

9. Which of the following is NOT correct?
Answer: *D*

A. Correct. WHO recommended tenofovir or entecavir as high barrier to drug resistance to all adult, adolescents and children aged 12 years or older. Only entecavir is recommended in children.
B. Correct. Nas with a low barrier, such as lamivudine and adefovir are not recommended because of drug resistance.
C. Correct. Generally, life-long antiviral therapy is required for HBV treatment.
D. Incorrect. Discontinuation of NAs is not recommended for persons with clinical evidence of cirrhosis. Discontinuation of NAs may be considered in some persons without cirrhosis.

10. Which is NOT correct regarding monitoring during treatment of HBV infections?
Answer: *D*

A. Correct. WHO recommended annual monitoring of ALT, HBsAg, HBeAg, HBV DNA, Adherence and drug toxicity.
B. Correct.
C. Correct. More frequent monitoring is recommended in those who do not clearly meet criteria for treatment and following after treatment discontinuation.
D. Incorrect. Every 6 months monitoring is recommended in a patient with cirrhosis and family history of HCC.

11. Which of the following is NOT correct?

Answer: *B*

A. Correct. All HIV/HBV co-infected individuals should receive antiretroviral therapy regardless o CD4 count, because the co-infection related to more rapid progression and higher risk of HCC than HBV mono-infection.

B. Incorrect. Persons with HBV/HCV co-infection are at risk for HBV reactivation during and following HCV treatment. In some cases, HBV treatment should be started to prevent HBV reactivation after assessment for HBV treatment eligibility before HCV treatment initiation.

C. Correct.

D. Correct. Some drugs using as anti-retroviral treatment shows interaction with HCV direct anti-viral drugs The interaction should be checks before HCV treatment.

12. Based on the 2018 WHO hepatitis C treatment guidance, among the groups below, which one should be considered "highest priority" for hepatitis C treatment?

Answer: *B*

A. Incorrect. Concurrent treatment of HCV infection and tuberculosis must be avoided because of drug interaction. Active TB involves a risk of secondary transmission and that can be life-threatening in a shorter time frame than HCV. Thus, TB is usually treated as a priority before starting HCV treatment.

B. Correct. Persons with HIV/HCV coinfection generally have more rapid disease progression than mono-infected persons.

C. Incorrect. PWID are at increased risk of new HCV infection and reinfection. They require prevention services to reduce risk of infection and reinfection after a cure. HCV treatment is necessary, however, the priority for treatment are people living with HIV/HCV coinfection.

D. Incorrect. Type 2 diabetes mellitus is one of extrahepatic manifestation of chronic HCV infection.

13. Based on the 2018 WHO hepatitis C treatment guidance, which one of the following is pan-genotypic regimen for hepatitis C treatment?

Answer: *D*

A. Incorrect. Genotype-specific treatment (G1, 4, 5 and 6)

B. Incorrect. Genotype-specific treatment (G2 and 3)

C. Incorrect. Combination of simeprevir is incorrect.

D. Correct. Pan-genotypic regimens are combinations of sofosbuvir and velpatasvir, sofosbuvir + daclatasvir, glecaprevir + pibrentasvir

Training workshop on screening diagnosis and treatment of hepatitis B and C
Organized by _____
Venue _____ on (days), (month), (year).

OBJECTIVES:

1. Participants are oriented to screening, diagnosis and treatment of hepatitis B and C.
2. Prepare participants to effectively deliver care and treatment of people living with hepatitis B and C, as part of national public health response to combating viral hepatitis.

Day 1: (date), (month), (year).

Time	Topic	Objectives	Facilitator/Trainer
0830 – 0900	Registration of participants		
0900 – 0910	Welcome to participants		
0910 – 0920	Objectives of the training		
0920 – 0940	Introduction of participants	Get to know each other	
0940 – 1000	Pre-workshop questionnaire		
1000 – 1030	Overview of viral hepatitis: national	To be adapted accordingly, including national overview	
1030 – 1100	Liver: structure and functions	Refresh basic understanding	
1100 – 1115	Tea/coffee break		
1115 – 1215	Liver injury: causes, signs and symptoms	Refresh and introduce terms including acute hepatitis, chronic hepatitis, liver cirrhosis, liver failure etc.	
1215 – 1230	Group photograph		
1230 – 1345	Lunch		
1345 – 1415	Interpretation of liver function tests		
1415 – 1515	Transmission and prevention (except vaccination) with focus on hepatitis B and C		
1515 – 1530	Tea/coffee break		
1530 – 1615	Hepatitis B vaccination and prevention of mother to child transmission		
1615 – 1645	Natural history of hepatitis C infection		
1645 – 1715	Testing and serological markets of hepatitis C infection		
1715 – 1730	Question/clarifications: Day 1		

Training workshop on screening diagnosis and treatment of hepatitis B and C
Organized by _____
Venue _____ on (days), (month), (year).

OBJECTIVES:

1. Participants are oriented to screening, diagnosis and treatment of hepatitis B and C.
2. Prepare participants to effectively deliver care and treatment of people living with hepatitis B and C, as part of national public health response to combating viral hepatitis.

Day 2: (date), (month), (year).

Time	Topic	Objectives	Facilitator/Trainer
0900 – 0915	Recap Day 1, questions and clarifications		
0915 – 0945	Natural history of hepatitis B infection		
0945 – 1030	Testing and serological markers of hepatitis B infection		
1030 – 1100	Non-invasive markers of chronic liver disease (e.g. APRI, FIB-4, FibroTest)		
1100 – 1130	Tea/coffee break		
1130 – 1245	Clinical management of Hepatitis C infection I		
1245 – 1345	Lunch		
1345 – 1430	Clinical management of Hepatitis C infection II	Include special situations and groups	
1430 – 1530	Clinical management of hepatitis B infection I		
1530 – 1545	Tea/coffee break		
1545 – 1700	Clinical management of hepatitis B infection II	Include special situations and groups	
1700 – 1715	Question and clarifications: Day 2		

Training workshop on screening diagnosis and treatment of hepatitis B and C
Organized by _____
Venue _____ on (days), (month), (year).

OBJECTIVES:

1. Participants are oriented to screening, diagnosis and treatment of hepatitis B and C.
2. Prepare participants to effectively deliver care and treatment of people living with hepatitis B and C, as part of national public health response to combating viral hepatitis.

Day 3: (date), (month), (year).

Time	Topic	Objectives	Facilitator/Trainer
0900 – 0915	Recap Day 2, questions and clarifications		
0915 – 1000	Practice session I: from classroom to patient care [Decide mode of learning. Examples include video from another room where doctor interacts with patients, grand rounds in wards, recorded videos, patient expert]		
1000 – 1045	WHO M&E Framework for viral hepatitis and patient monitoring	Understand M&E framework and data reporting. To adapt according to national reporting systems	
1045 – 1115	Tea/coffee break		
1115 – 1200	Practice session II [Decide mode of learning, including case studies]		
1215 – 1230	Questions and clarifications		
1230 – 1245	Closing remarks		
1245 – 1315	Post-training questionnaire, evaluation of the workshop		
1315 -1330	Distribution of certificates		
1330	Lunch and close of workshop		

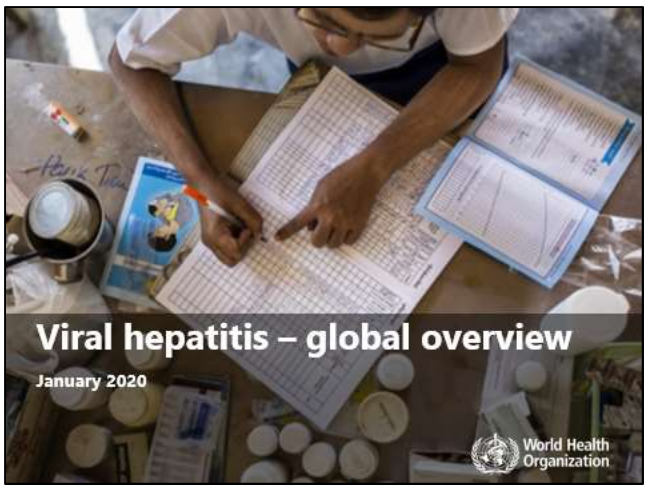
Note to trainers: Some principles of training and adaptation to training needs:
1. Ensure training is tailored for the level of the audience/participants for training
2. Update and contextualise the modules according to new and country data
3. Sessions should not be more than 30 min each time, allow for breaks
4. Summarise or have “take home” messages at the conclusion of the session
5. Allow adequate time for questions and answers
6. Get feedback from participants to improve the training
7. Pre and post tests are useful tools to document the state of knowledge and immediate output of the training

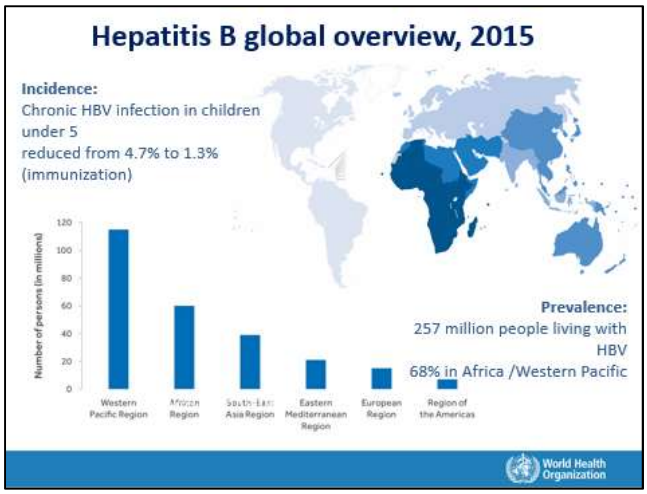
Note: trainers should review the modules, and update the information according to current guidelines, national guidelines and evidence as appropriate. Some modules such as the M&E module will require country adaptation according to the hepatitis data reporting systems.

Module 1A

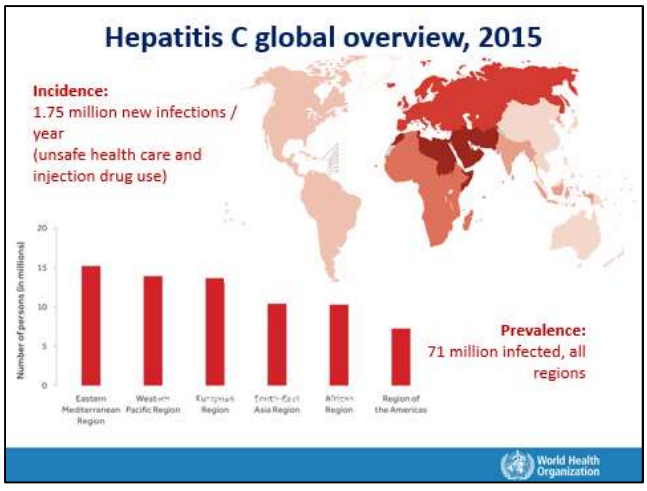
Overview of viral hepatitis: global progress update

Module 1A

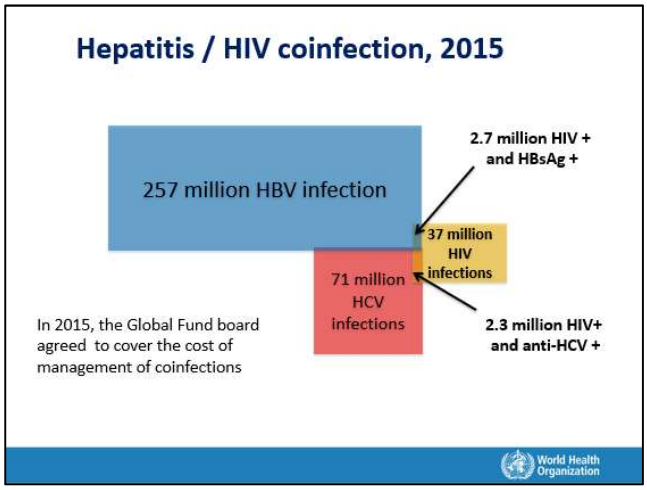




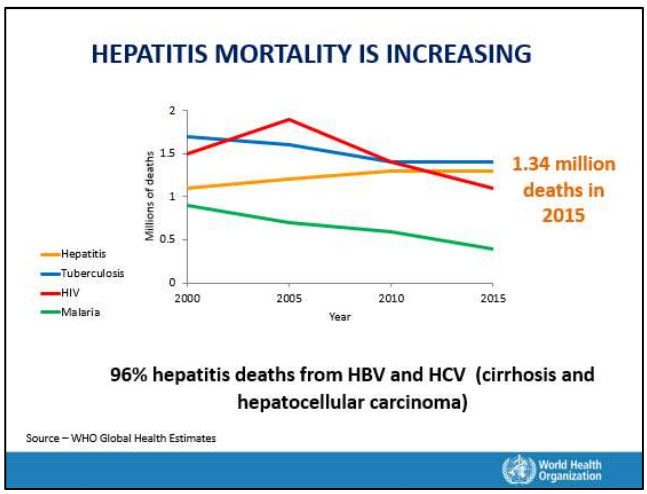
This slide shows the epidemiological situation of hepatitis B. The map on the right-hand side shows the cumulative incidence of chronic HBV infection in children under five as represented by the prevalence of hepatitis B surface antigen. This cumulative incidence of chronic HBV infection in children under 5 years fell from 4.7% in the pre-vaccine era to 1.3% in 2015. This considerable reduction of incidence is attributable to progress in immunization coverage. On the graph at the bottom of the slide, you can see the number of people living with HBV in the various WHO regions. There are 257 million persons living with HBV in the world 68% of these are living in the African or in the Western Pacific regions.



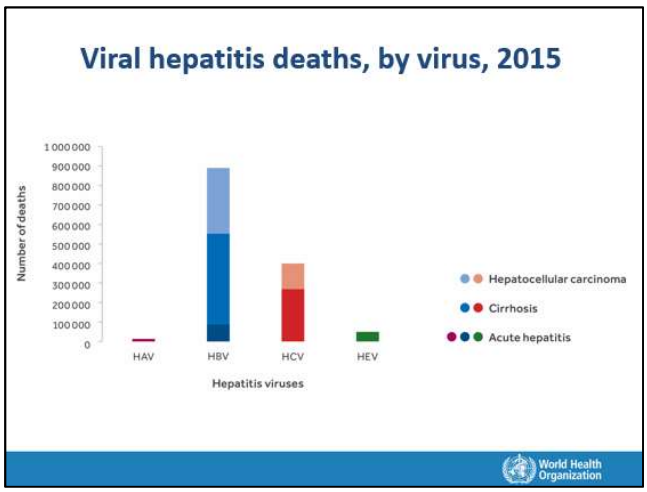
This slide shows the epidemiological situation of HCV infection. The map at the top shows the incidence of HCV infection by WHO region. Overall, there are still 1.75 million new infections in the world each year. This is more than the number of persons who were cured in 2015 – indicating a growing epidemic. Unsafe health-care injections and injection drug use still cause transmission of HCV in many hotspots, particularly in the Eastern Mediterranean and European regions. At the bottom of this slide, you can see the total number of persons living with HCV infection by region; 71 million of persons are living with HCV. The number of persons with HCV infection is about the same in all regions, but there are differences across countries and sometimes within countries.



HIV- Hepatitis B coinfections are estimated at 2.7 million
HIV- Hepatitis C coinfections are estimated at 2.3 million



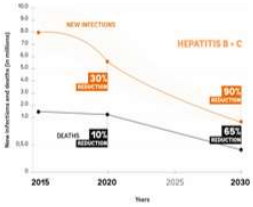
If we look at mortality, we see that over the last 10 years, for HIV, tuberculosis and malaria, the numbers have decreased. For hepatitis, the orange line, you will note that mortality is increasing, with 1.34 million deaths in 2015. 96% of the mortality from viral hepatitis is attributable to the sequelae of HBV and HCV infections, which include cirrhosis and hepatocellular carcinoma. How were we doing in 2015 to reverse that trend? Let's review together the status of the various core interventions of the global strategy.



The majority of death is attributable to chronic infection with hepatitis B or C

Global Strategy on Viral Hepatitis Elimination (2016–2021)

In 2016, during the World Health Assembly, Member States endorsed the Global Strategy on Hepatitis that called for elimination of hepatitis as a public health threat by 2030



SDG 3.3

Goal = Eliminate viral hepatitis as a major public health threat by 2030

World Health Organization

The World Health Assembly pledged to reach elimination

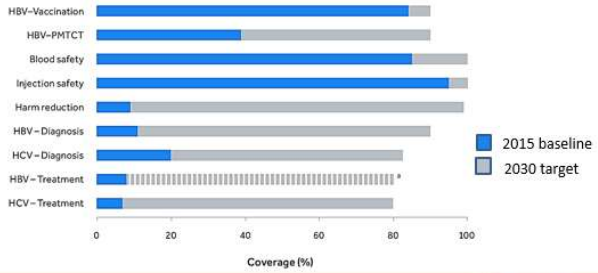
5 core interventions with sufficient coverage would lead to elimination (incidence – 90%, mortality – 65%)

	Interventions	Indicator	2015	2020	2030
	3 doses of HBV vaccine	Coverage	84%	90%	90%
	HBV PMTCT	Coverage	39%	50%	90%
	Blood / injection safety	Screened donations	97%	100%	100 %
		Safe injections	95%	100%	100%
	Harm reduction	Sets/PWID/year	27	200	300
	HBV and HCV testing and treatment	% diagnosed	9/20%	30%	90%
		% treated	8/7%	N/A	80%

World Health Organization

Baseline estimates of the coverage of core interventions, 2015

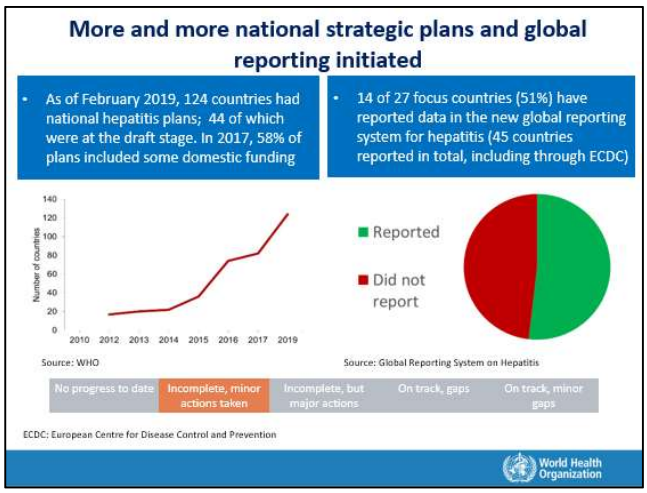
Major gaps in HBV birth dose, harm reduction, testing and treatment



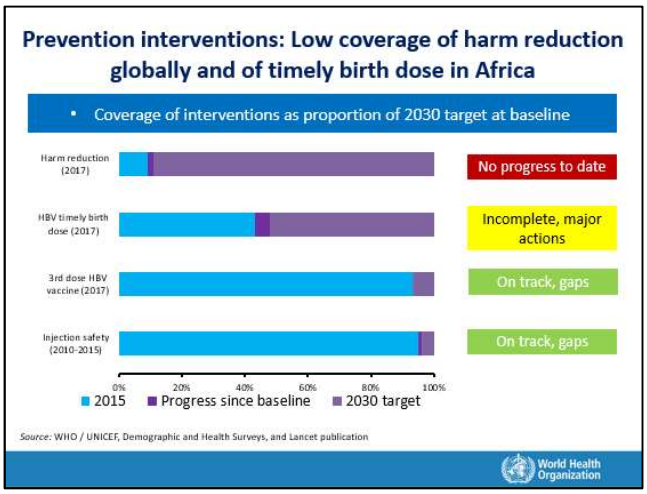
World Health Organization

As a baseline at 2015, there is major gaps in the global response to hepatitis action in HBV birth dose, harm reduction, testing and treatment. We have a long way to go towards elimination of viral hepatitis as a public health threat by 2030.

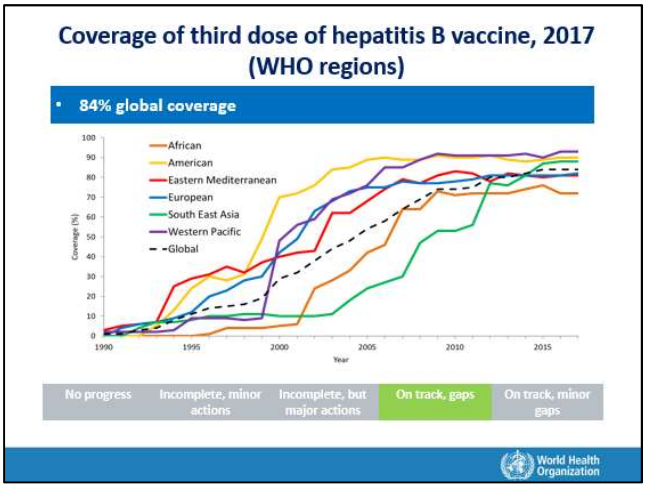
WHO has delivered most of the global goods needed to guide national action on viral hepatitis elimination



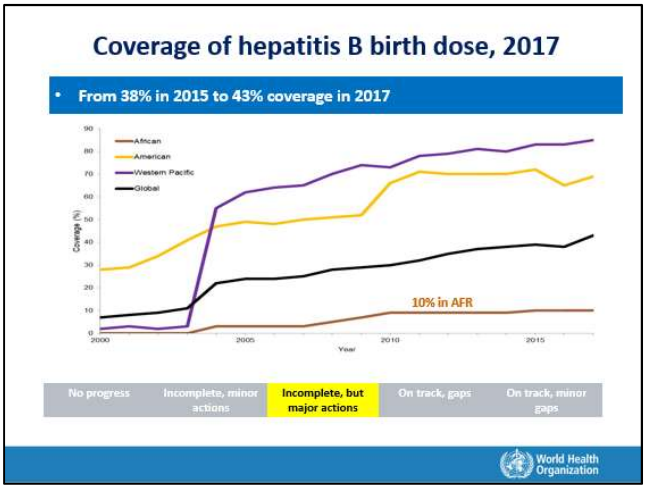
More and more countries are working on comprehensive national action plans for viral hepatitis. WHO has established the new global reporting system for hepatitis, and more countries are reporting into this system



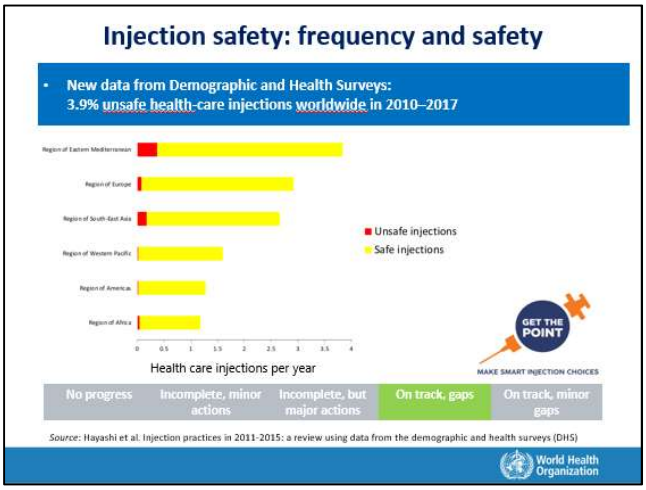
Module 1A



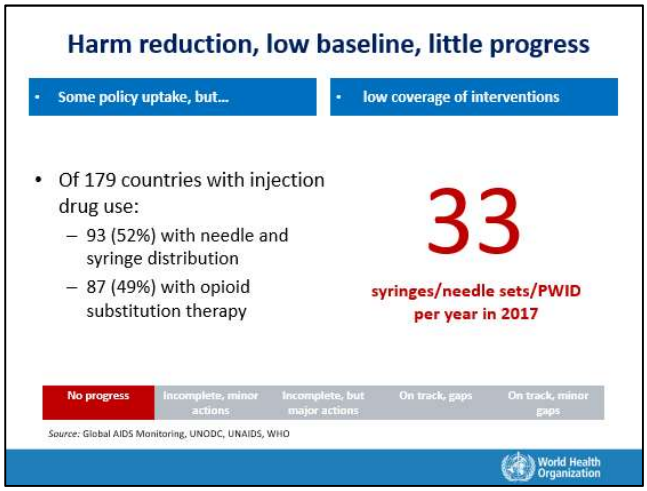
First in terms of hepatitis B vaccine we have seen major progress since 2000, with 84% global coverage for the third dose in 2015. High vaccine coverage successfully reduces incidence in children. However, to reduce the incidence of these infections acquired at birth, which are most at risk for progression towards chronic liver diseases, another intervention is needed.



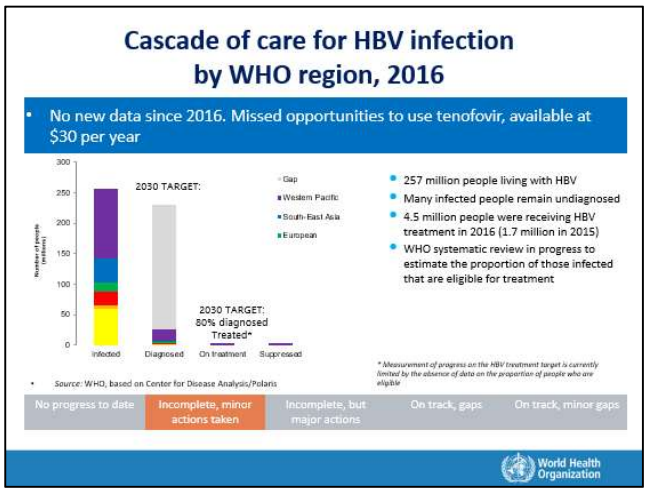
That other intervention is the birth dose. On the slide, you can see the coverage of the birth dose of hepatitis B vaccine between 2000 and 2015 for selected regions. We have had success stories in the Western Pacific region where perinatal transmission was a major problem. In the Americas, coverage tremendously increased also. However, global coverage (as a dashed black line) is still low at 39% and in the African region which is highly endemic for hepatitis B, the coverage of the timely birth dose is only 10%.



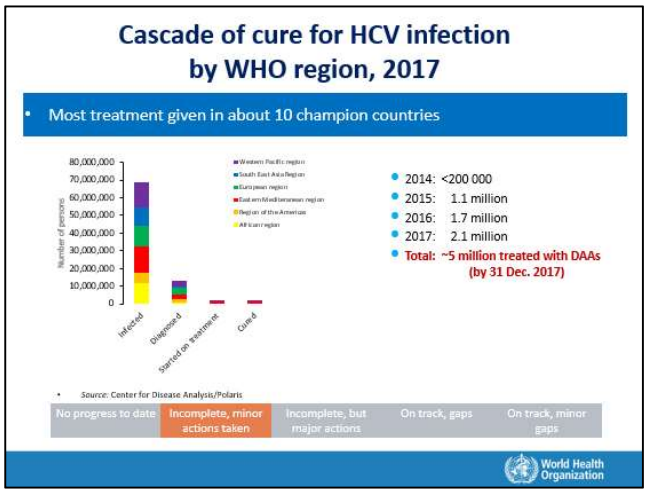
This graph shows health care injections per year and the red graph shows unsafe injections. Unsafe injections is an important element. The goal is to have 100% safe injections (or, conversely 0% unsafe injections)



For comprehensive harm reduction services in the context of policies that prevent stigma and discrimination, we are far from the target. By 2030, we should be at 300 needle and syringe sets per person and per year. However of the 11.8 million persons who inject drugs worldwide, on the left hand side, too few have access to satisfactory harm reduction services. Our estimated number of needle/ syringe distributed per person who inject drugs per year is low at 33 while we should reach at least 200 by 2020 (On the right hand side).

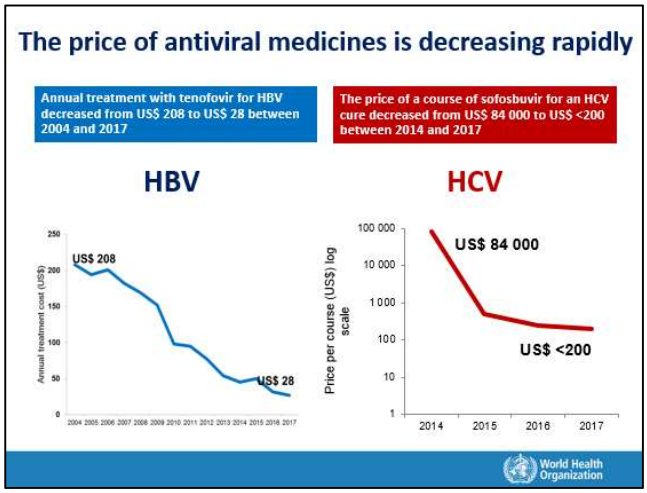


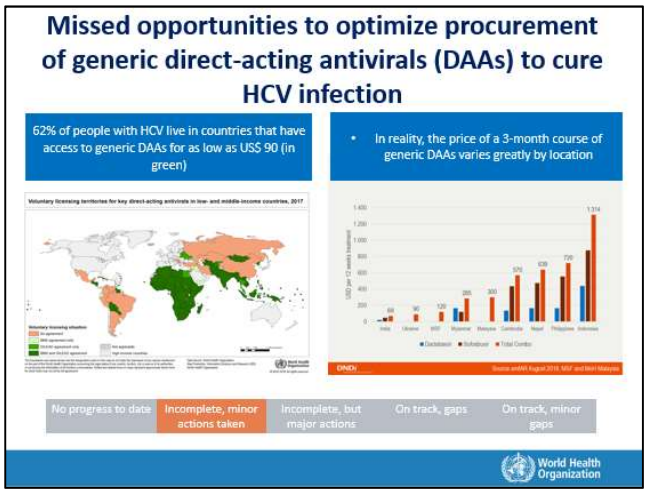
Let us look at testing and Treatment, what we call the cascade of care, first for HBV: many of the 257 million people living with chronic hbv remain undiagnosed, and even fewer, about 4.5 million were on treatment in 2016.

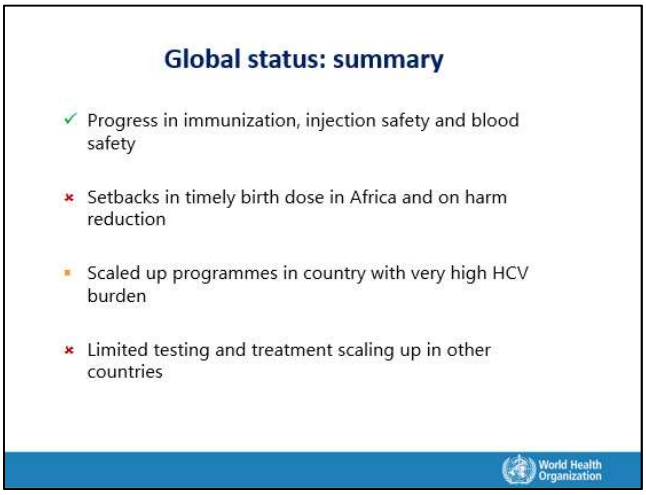


For HCV, we also have a major testing gap, in all parts of the world (shown in the diffèrent colours). At best, 20% are being diagnosed, and about 3 million people had received DAAs, cumulatively by 2017.

Module 1A





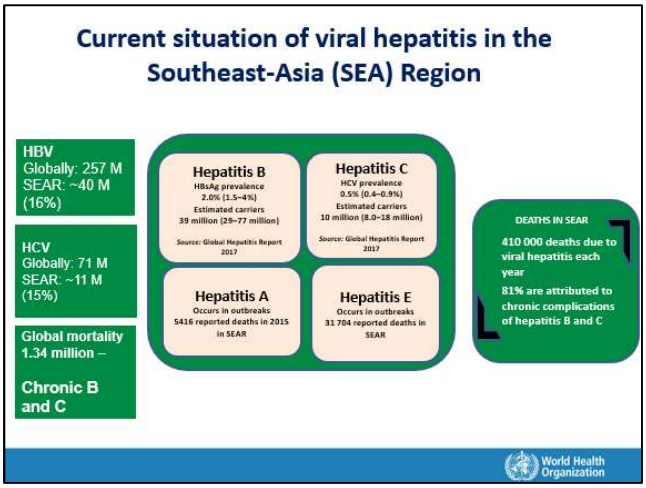


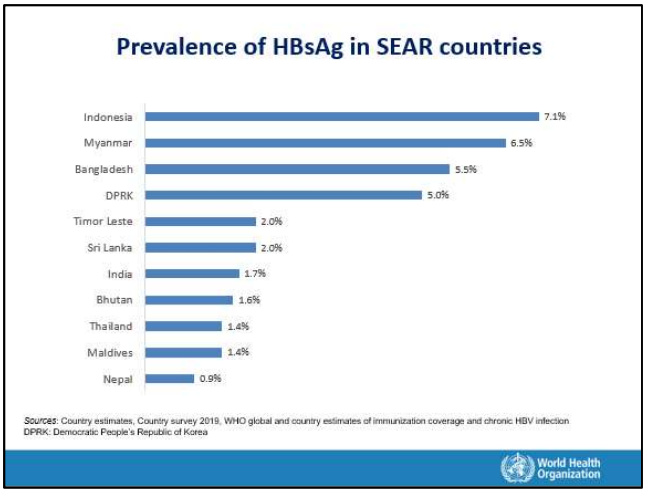
At present, we have a favourable environment to control viral hepatitis because the cost of highly effective drugs has been markedly reduced in the past decade, which has made hepatitis B and C treatment affordable for countries. Several countries are starting their national viral hepatitis control programmes. When treatment become highly effective and cheaper, it is more cost effective to treat a health condition en masse under the umbrella of a public health programme. Tenofovir is the main drug used for the treatment of hepatitis B and its cost has reduced by more than 10-fold in the past 15 years. Similarly, sofosbuvir is the backbone of hepatitis C treatment and its cost has reduced by more than 500-fold since it was first approved for use in 2014.


Way forward
Strengthen country support tailored to their unique contexts
Simplify to integrate with HIV, TB, Malaria, communicable and non-communicable diseases
Strengthen partnerships
Within WHO headquarters
With country and regions
With external partners
Advocate for implementation within the Universal Health Coverage (UHC) framework
World Health Organization

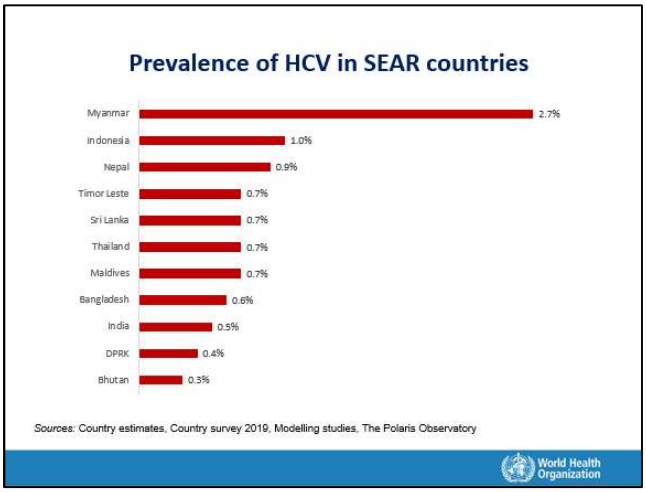
Module 1B

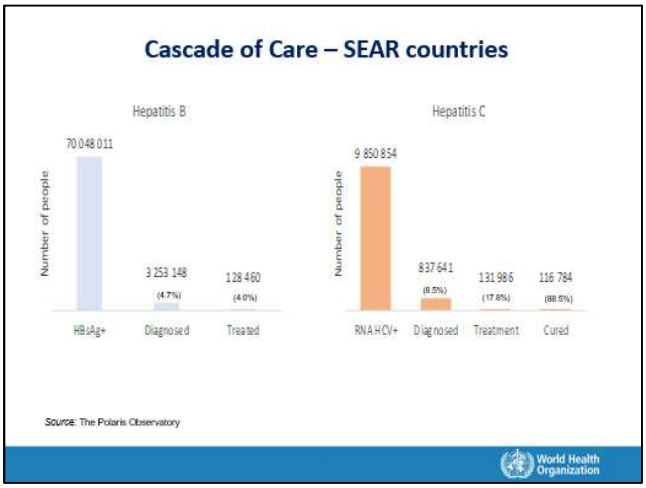
Global and SEAR situation overview

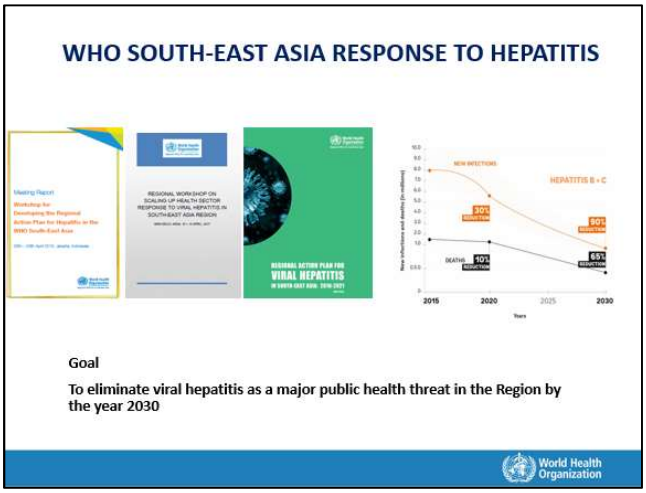




Hep B is heterogeneous in the Region and varies from low to moderate to high endemicity.







Goal
To eliminate viral hepatitis as a major public health threat in the Region by the year 2030

Module 1B

Regional (SEAR) Plan of Action

World Health Organization

Baseline estimates and key targets in the Regional Action Plan

Interventions	Indicator	SEAR baseline estimates	SEAR regional targets (2020)	Global targets (2020)
Hepatitis B vaccination	HEPB3 coverage	93%	95%	90%
HBV PMTCT	HEP vaccine birth-dose coverage	53%	90%	50%
Blood safety	Donations screened with quality assurance	85%	100%	95%
Injection safety*	Proportion of unsafe injections	5.2%	50%	100%
Harm reduction	Syringes & needles distributed/PWID/year	92	200	200
Testing services	% HBV-infected diagnosed	4.7%	50%	30%
	% HCV-infected diagnosed	8.5%	50%	30%
Treatment	% diagnosed with HBV on treatment	4.0%	75%	5 million
	% diagnosed with HCV started on treatment	17.8%	75%	3 million

*The target set for injection safety in the action plan is " 50% of all injections in Member States are administered with safety-engineered devices

Source: Global Hepatitis Report, 2017

World Health Organization

Progress towards implementing national plans for elimination of viral hepatitis

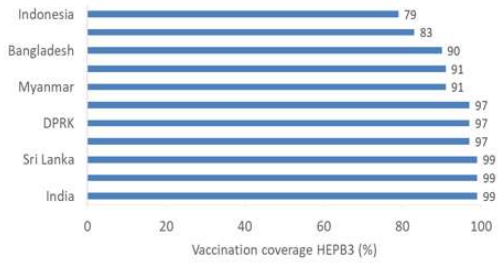
	Bangladesh	Bhutan	DPRK	India	Indonesia	Maldives	Myanmar	Nepal	Sri Lanka	Thailand	Timor Leste
National prevalence estimates†	×	↻	×	×	✓	×	✓	✓	×	×	×
National action plans for hepatitis	Drafted	Drafted	Drafted	Developed	Drafted	Drafted	Developed	Drafted	Drafted	Developed	Developed
National guidelines for testing*	×	×	✓	✓	✓	×	✓	✓	×	✓	✓
National guidelines for treatment*	×	×	×	✓	✓	×	✓	Drafted	×		✓

† national representative population-based estimates (e.g. seroprevalence survey)
*aligned with WHO guidelines

Source: Country survey 2019

World Health Organization

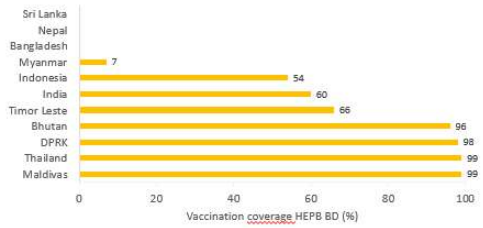
HEPB3 vaccination coverage 2018



Source: SEARO, 2018

World Health Organization

HEPB BD vaccination coverage 2018



Data source: 2018 WHO/UNICEF JRF country official estimates

World Health Organization

Blood and injection safety

	Bangladesh	Bhutan	DPRK	India	Indonesia	Maldives	Myanmar	Nepal	Sri Lanka	Thailand	Timor Leste
Screening of donated blood for HBV/HCV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Safe injection and IPC policy	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Hepatitis B screening for all pregnant women	✓	✓	✓	×	✓	✓	×	✓	×	✓	×
Harm reduction services for PWID	✓	×	×	✓	✓	×	✓	✓	×	✓	✓

Source: Country Survey 2019

Harm reduction services for PWID

	Bangladesh	Bhutan	DPRK	India	Indonesia	Maldives	Myanmar	Nepal	Sri Lanka	Thailand	Timor-Leste
Estimated PWID population size	34 000	-	-	177 000	33 500	-	93 000	30 900	2 700	42 000	-
Needles/syringes distributed/PWID/year	205	-	-	366 7	3	-	351	85	0	10	-
Percentage of PWID receiving OST	3.1%	-	-	16.5%	10.5%	-	17.2%	2.8%	-	5.3%	-

Source: UNAIDS – Key population atlas

World Health Organization

WHO's injection safety project

- WHO support in three countries (India, Egypt and Uganda)
- Technical support (national level and in Punjab state of India)
- Objectives:
  - Country support to the process
  - document the process from early adopter states
  - Disseminate information for programmatic use
- Focus on injection safety (yet, an opportunity to improve
  - infection prevention and control (IPC) practices
  - patient safety and quality of health care, and
  - Health-care waste management

World Health Organization

Number of testing facilities

Country	HEPATITIS B TESTING		HEPATITIS C TESTING	
	Serology (HBsAg)	NAT (HBV DNA)	Serology (anti-HCV)	NAT (HCV RNA)
Bangladesh	500	15	500	15
Bhutan	37	-	26	-
DPR Korea	136	-	136	-
India	-	-	-	-
Indonesia	-	-	-	-
Maldives	>20	1	>20	1
Myanmar	11 910	3	11 910	8
Nepal	100	1	100	1
Sri Lanka	2	2	2	2
Thailand	1 100	100	1100	100
Timor-Leste	6	1	-	-

Source: Country survey 2019

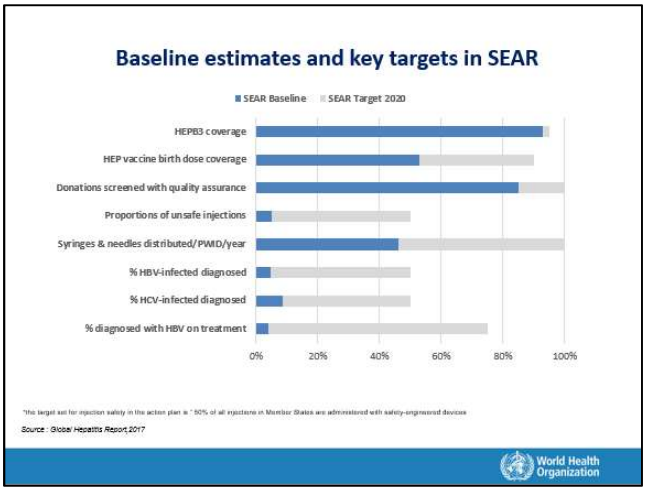
World Health Organization

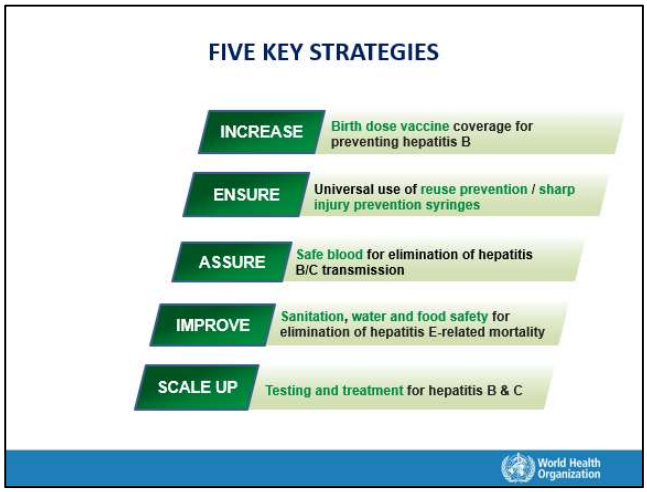
Treatment available and cost

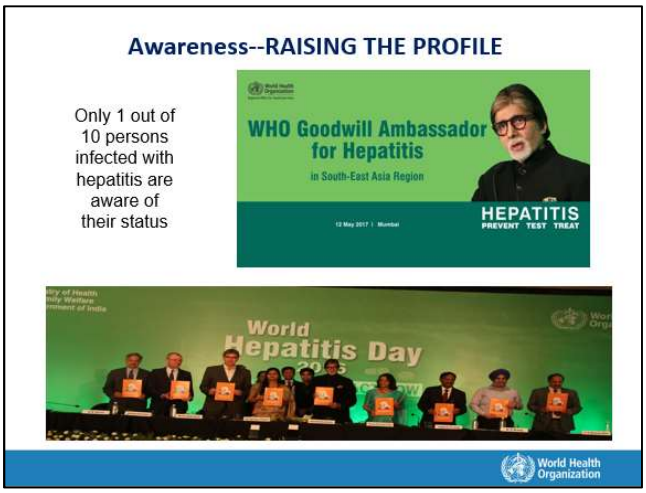
Country	Hepatitis B treatment		Hepatitis C treatment	
	Treatment available	Annual cost per patient (US$)	Treatment DAA available	12 weeks cost per patient (US$)
Bangladesh	✓	360	✓	1000
Bhutan	-	-	-	-
DPR Korea	-	-	-	-
India	✓	45	✓	40
Indonesia	✓	-		450
Maldives	✓	-	x	-
Myanmar	✓	184	✓	93
Nepal	✓	400	✓	600
Sri Lanka	x	-	x	500
Thailand	✓	-	✓	-
Timor-Leste	x	-	x	-

Source: Country Survey 2019

World Health Organization


Baseline estimates and key targets in SEAR
SEAR Baseline
SEAR Target 2020
HEPB3 coverage
HEP vaccine birth dose coverage
Donations screened with quality assurance
Proportions of unsafe injections
Syringes & needles distributed/PWD/year
% HBV-infected diagnosed
% HCV-infected diagnosed
% diagnosed with HBV on treatment
0%
20%
40%
60%
80%
100%
Source : Global Hepatitis Report,2017
World Health Organization


FIVE KEY STRATEGIES
INCREASE
Birth dose vaccine coverage for preventing hepatitis B
ENSURE
Universal use of reuse prevention / sharp injury prevention syringes
ASSURE
Safe blood for elimination of hepatitis B/C transmission
IMPROVE
Sanitation, water and food safety for elimination of hepatitis E-related mortality
SCALE UP
Testing and treatment for hepatitis B & C
World Health Organization


Awareness--RAISING THE PROFILE
Only 1 out of 10 persons infected with hepatitis are aware of their status
WHO Goodwill Ambassador for Hepatitis
in South-East Asia Region
HEPATITIS
PREVENT TEST TREAT
World Hepatitis Day
World Health Organization

Key challenges

- National and representative burden of disease still not known in many countries
- Know your epidemic – asymptomatic nature of illness – early identification remains an issue;
  - Only 10% of infected people know their status
- National plans for viral hepatitis are still in draft stage in most of countries
- Governance issues – need for multisectoral response – immunization, blood and injection safety, etc.
- Addressing hepatitis among KPs – harm reduction among PWID a challenge
- Unsafe injections continue to be an issue
- Stigma widespread and continues
- Lack of wide availability of RDT, limited lab capacity; whom to prioritize for testing
- Lack of access to cheaper drugs in some countries
- Lifelong therapy for HBV, lack of dedicated catalytic funds unlike HIV

World Health Organization

WHO SEARO-Sustain-Accelerate-Innovate is the Mantra

Sustain the momentum and willingness in countries to have national action plans	• Focus on data generation and use of cost–effectiveness tools for advocacy • Continue to provide technical support to countries to develop and implement national action plans • Advocacy for national funding using hep B calculator, investment case
Accelerate implementation of activities for elimination of hepatitis	• Accelerate the implementation of national action plans for hepatitis o Accelerate adoption of rapid tests for hepatitis testing o Accelerate birth dose immunization for Hep B o Accelerate use of reuse-prevention syringes o Build capacity of health force at primary and secondary levels o Do not lose focus on A and E – safe water and hygiene • Periodically review the progress on hepatitis action plan implementation
Innovate Sustainability of interventions	• Newer tools for finding the missing millions infected with hepatitis • Integrated service delivery models for efficient use of resources

World Health Organization

RESPONSIVE LEADERSHIP

"Identifying interventions that have a high impact is a key step towards eliminating this devastating disease. Many countries have succeeded in scaling-up the hepatitis B vaccination. Now we need to push harder to increase access to diagnosis and treatment."

Dr. Tedros Adhanom Ghebreyesus
Director General, WHO

"We need strong political commitment and speedy and innovative implementation of the South-East Asia Regional Action Plan for hepatitis in an integrated manner. We are also committed to support Member States in developing their national action plans for prevention and control of hepatitis."

Dr. Poonam Khetrapal Singh
Regional Director, WHO South-East Asia

World Health Organization

Module 1C

Viral hepatitis in the Western Pacific region

Module 1C

Learning objectives

At the end of this session, participants will be able

- to demonstrate improved knowledge of regional epidemiology of viral hepatitis
- to understand the regional response and strategies to combat hepatitis

World Health Organization

Elimination of Viral Hepatitis in the Western Pacific Region

January 2020

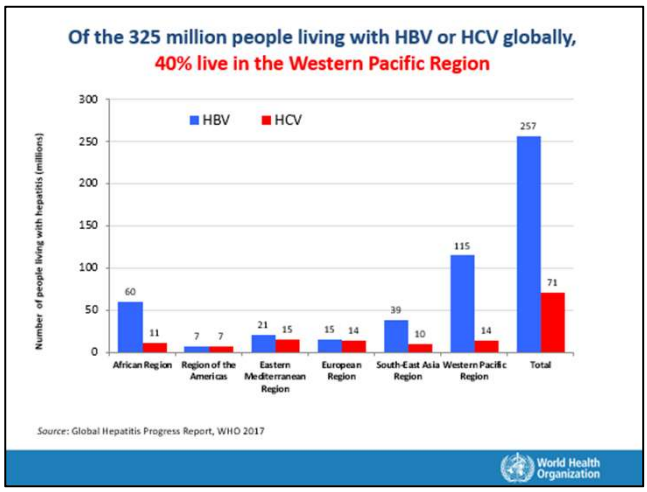
World Health Organization

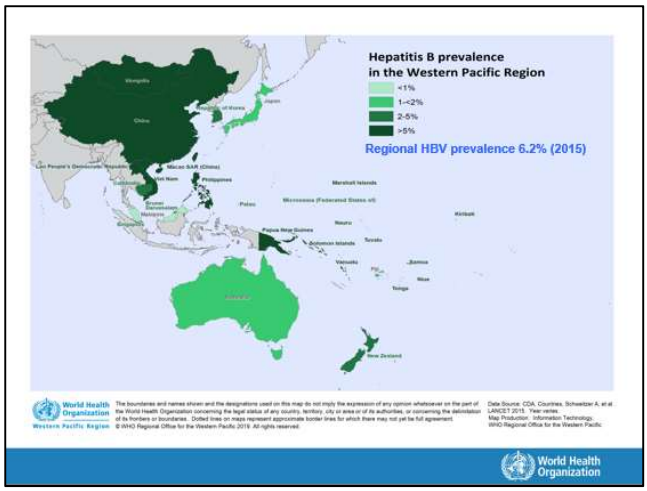
Outline

- Overview: current situation
- Implementing towards elimination: progress
- Future directions

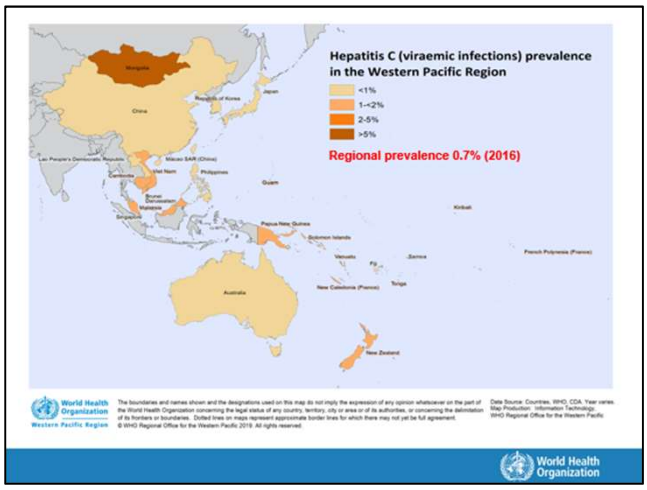
World Health Organization

Module 1C



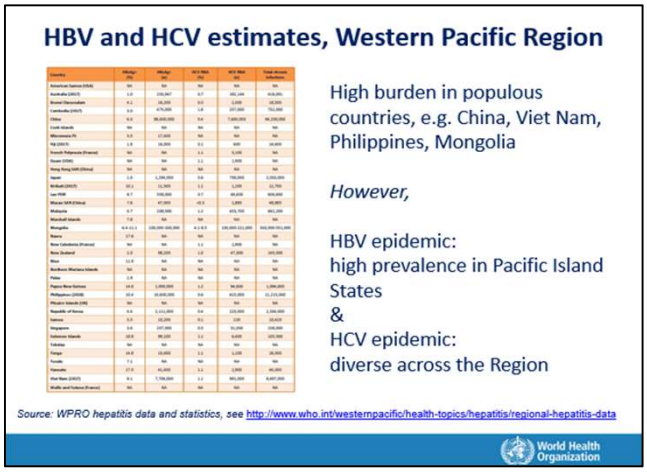


There is large diversity of the burden of hepatitis B in the Western Pacific Region. Many of the countries in the Pacific region (small island states) bear a high burden of hepatitis B (where prevalence of HBV is > 5%)



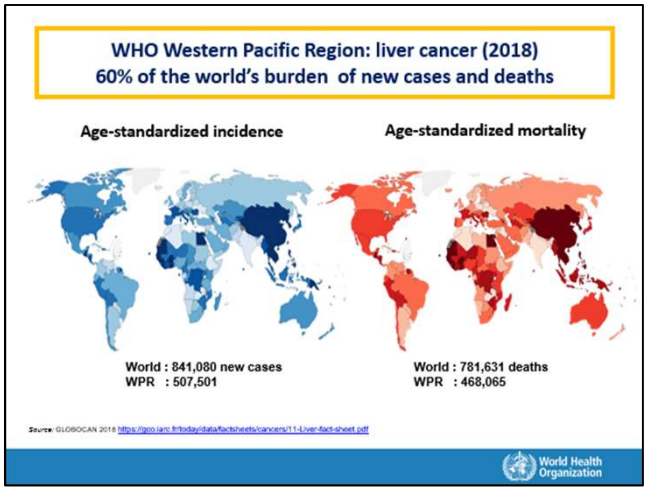
The Hepatitis C prevalence is variable across countries in the Region, and also within countries. The main drivers for hepatitis C are unsafe injections, injecting drugs use, and from unsafe blood (previously). Mother to child transmission is also a route of transmission but at low levels.

Module 1C



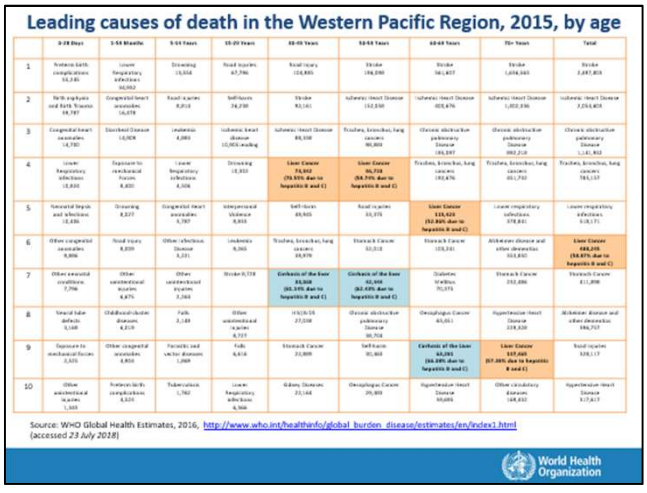
In the Western Pacific Region, HBV is endemic in several countries such as China, Papua New Guinea, Republic of Korea, Mongolia and Lao People's Democratic Republic.

HCV is endemic in Mongolia.
As compared to HCV, HBV is much more common in WPR countries.



Source: GLOBOCAN 2018. Link: https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf (Accessed 14 January 2020)

WPR has the highest burden of liver cancer globally, accounting for 60.3% of new cases of liver cancer and 60% of liver cancer deaths worldwide.
Most liver cancer is related to chronic hepatitis B or C.

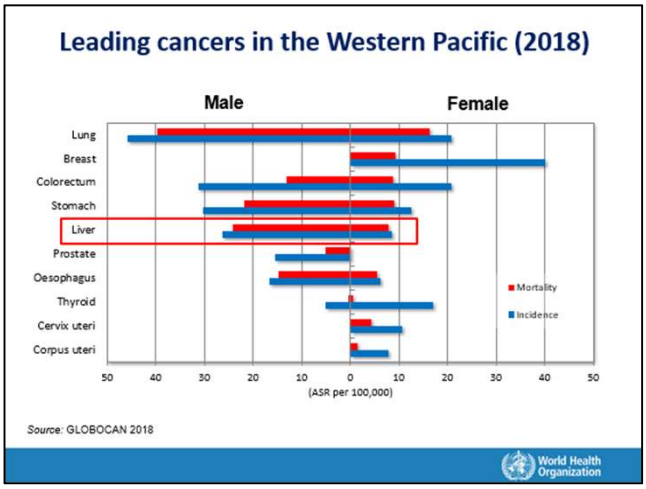


Let's look further in the impact of chronic hepatitis infection to health in the Region:

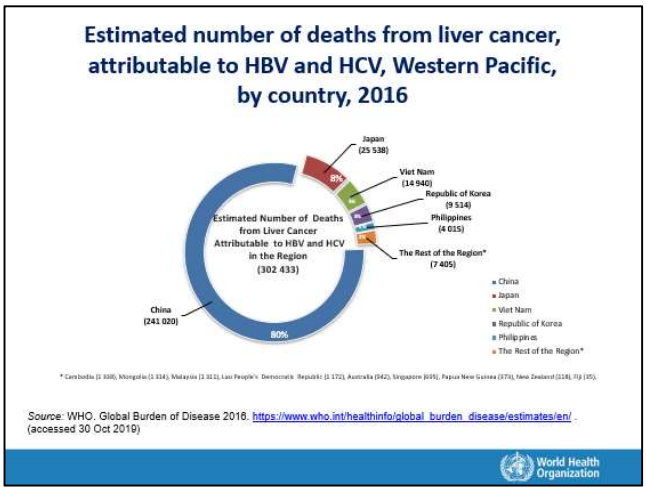
- We see that cirrhosis and liver cancer is already an issue from ages 30 years and above
- We know that the risk of cancer increases with age and this is evident as liver cancer is within the top 10 leading causes of death in the region
- Overall in WPR, liver cancer is the 6th top cause of deaths

These deaths, including related morbidity, is preventable. Earlier Treatment can prevent liver cancer

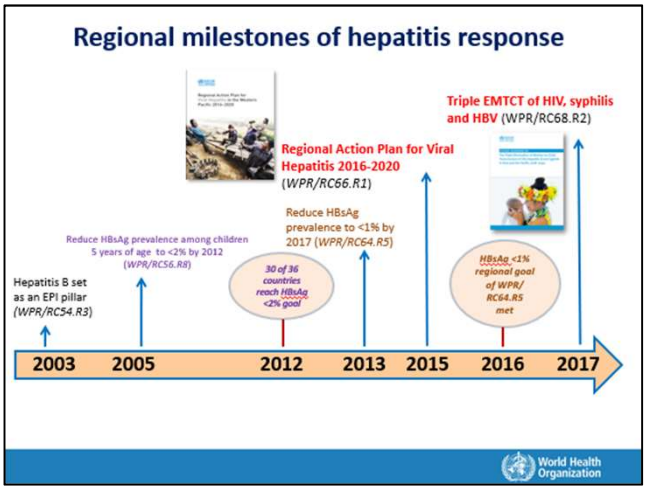
Module 1C



- Liver cancer is the 6th most common cancer worldwide; 5th in the Western Pacific region
- Liver cancer in the Western Pacific Region countries are mostly due to chronic hepatitis B or C infection, and can be prevented by treatment of those infected with hepatitis.
- Hepatitis C can be cured with effective direct acting antiviral combinations, while Hepatitis B can be effective treated with use of highly effective antivirals drugs.



This shows the number of death from liver cancer, attributable to HBV and HCV in the Western Pacific Region, 2016, by country. In term of numbers, China has the largest numbers because of the large population size.

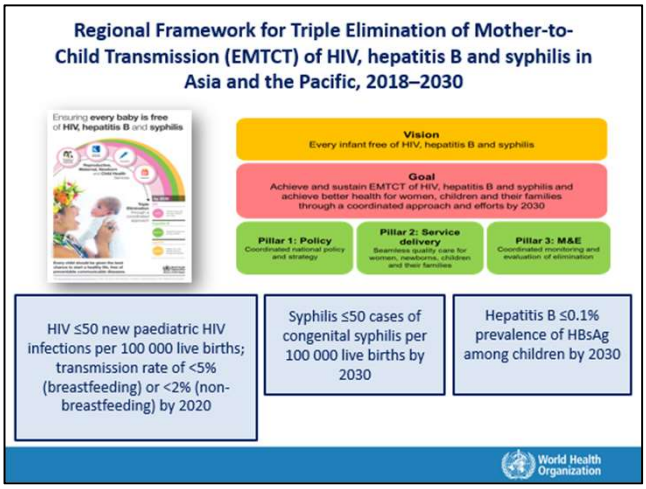


The Western Pacific Region has led the combat on hepatitis since the start with immunisation, moving EPI targets to achieve, and in 2015 – countries endorsed a comprehensive approach to elimination of hepatitis as public health threats, including prevention care and treatment.

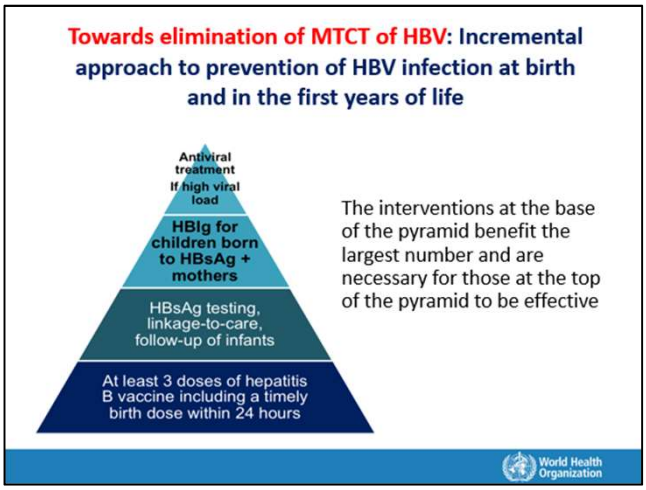
In 2017, building on the progress achieved in the region, the framework for triple elimination of mother to child transmission of HIV, hepatitis B and syphilis was endorsed

Note: immunization targets are for reduction of HBsAg prevalence among children 5 years of age

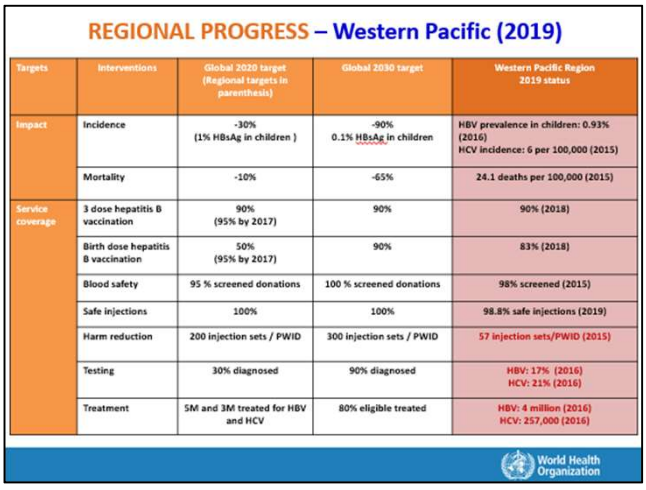
Module 1C



The triple elimination framework has a clear vision, goals and targets to be achieved. This framework piggybacks on the existing dual elimination, with HBV elimination added on. The ultimate target for HBV is 0.1% prevalence among children by 2030.



Taking the incremental approach, and building from the foundation of the immunization programme, working upwards through improving access to testing, linkage to care and follow up, and antiviral drug use for some women who have high viral load – so as to work towards an "almost zero infection".



Targets	Interventions	Global 2020 target (Regional targets in parenthesis)	Global 2030 target	Western Pacific Region 2019 status
Impact	Incidence	-30% (1% HBsAg in children)	-90% 0.1% HBsAg in children	HBV prevalence in children: 0.93% (2016) HCV incidence: 6 per 100,000 (2015)
	Mortality	-10%	-65%	24.1 deaths per 100,000 (2015)
Service coverage	3 dose hepatitis B vaccination	90% (95% by 2017)	90%	90% (2018)
	Birth dose hepatitis B vaccination	50% (95% by 2017)	90%	83% (2018)
	Blood safety	95 % screened donations	100 % screened donations	98% screened (2015)
	Safe injections	100%	100%	98.8% safe injections (2019)
	Harm reduction	200 injection sets / PWID	300 injection sets / PWID	57 injection sets/PWID (2015)
	Testing	30% diagnosed	90% diagnosed	HBV: 17% (2016) HCV: 21% (2016)
	Treatment	5M and 3M treated for HBV and HCV	80% eligible treated	HBV: 4 million (2016) HCV: 257,000 (2016)

Shown here are the Global Health Sector Strategy for Viral Hepatitis (GHSS) 2016-2021 service and impact targets. Targets for 2020 include getting 3 dose hep B vaccine coverage to 90% and hep B birth dose coverage to 50%. Also, GHSS looks to reduce the incidence to 1% in children by 2020 and to 0.1% by 2030.
The Western Pacific Region has met the prevention targets for the region and for global level. However, the main gap is in harm reduction, testing and treatment.

Note: Mortality rate: highest in the WPRO region (24.1 deaths per 100,000) followed by SEAR region (21.2 per 100,000). The global average death rate is 18.3 per 100,000.

Source: HBV vaccination: WHO Global and regional immunization profile (data as of 01 Dec 2019)
Link: https://www.who.int/immunization/monitoring_surveillance/data/gs_wprprofile.pdf?ua=1

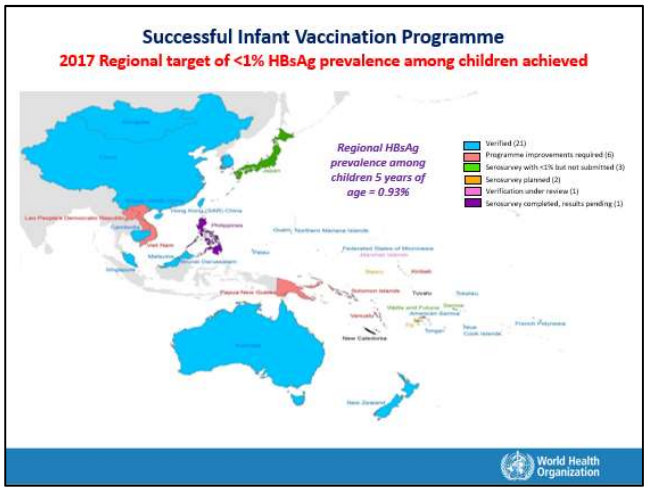
Blood safety: WHO. Global Status Report on Blood Safety and Availability, 2016

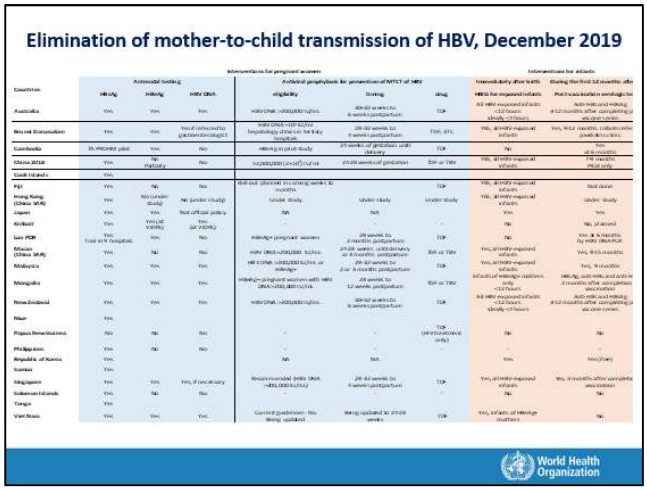
Safe injections: Safe injections as defined as "use of an unopen syringe or needle". Unsafe injections per person per year in WPRO =0.019 Hayashi T et al. Injection practices in 2911-2015L a review using data from the demographic and health surveys (DHS). BMC Health Services Research (2019)19:600

Harm reduction among people who inject drugs: https://aidsinfo.unaids.org/
Indicator: Number of needles per person who inject drugs
Note – in 2018, there was no data estimated for the region, but data is available in several countries:

Testing and Treatment: Modelling estimates 2016 from WHO/CDA Foundation

Module 1C

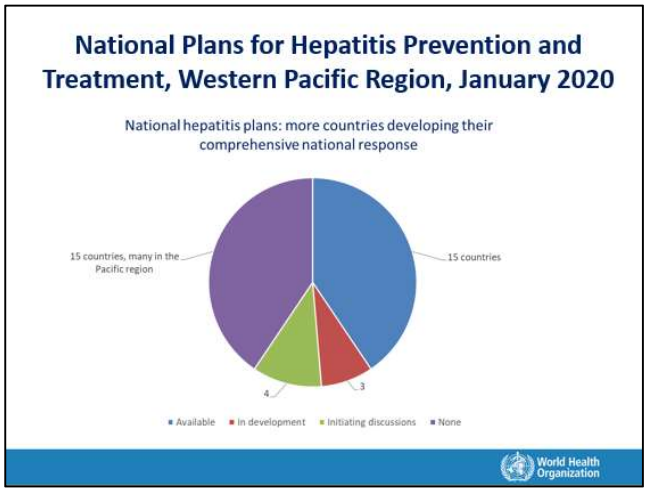




As more countries achieve the target of <1% HBsAg among children under 5 years of age, there is new interventions to further reduce the risk of mother to child transmission particularly among infants born to HBV-infected pregnant women. The Framework for triple elimination of HIV, syphilis and hepatitis B calls for coordinated delivery of integrated services for preventing mother to child transmission. Interventions consists of antenatal testing for HBV, antiviral prophylaxis for prevention of MTCT of hepatitis B among pregnant women who need it. The WHO guidelines for use of antiviral drugs among pregnant women infected with hepatitis B and the criteria to start is under development, and will be released in 2020. Among HBV exposed infants, providing the timely birth dose of HBV vaccines within 24 hours is essential. HBIG use is recommended as part of current standard guidelines, but may not be available or affordable in many low and income countries.

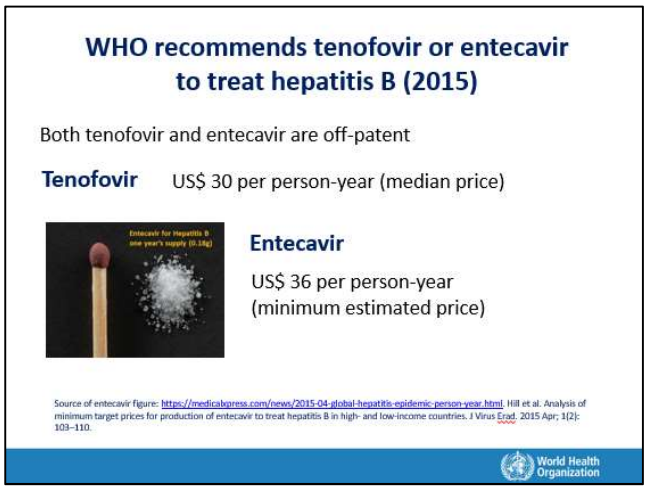
The table provides an overview of national guidelines or interventions delivered for HBV EMTCT in WPRO, as of December 2019

Module 1C



Beyond vaccination for hepatitis B as the prevention, to get towards hepatitis elimination by 2030, it is important to have national comprehensive strategic or action plans, which include both prevention and treatment. National Plans articulate the vision, goals and set targets to be achieved and funded for the country.

In the Western Pacific Region, which consists of 37 countries and territories, more and more countries are development their national plans for prevention and treatment

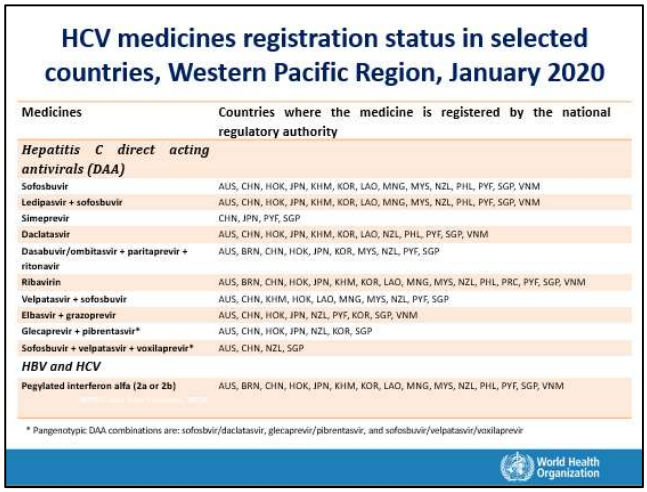


Hepatitis B medicines (tenofovir and entecavir) are available in all countries, in generic and originator options.
Tenofovir and entecavir are off-patent

The median prices for tenofovir globally is US$ 30 per person-year
For entecavir: this is estimated at US$ 36 per person year

The prices of both medicines are approaching similar prices as countries list both into their essential medicines list, and promote generic options for both.

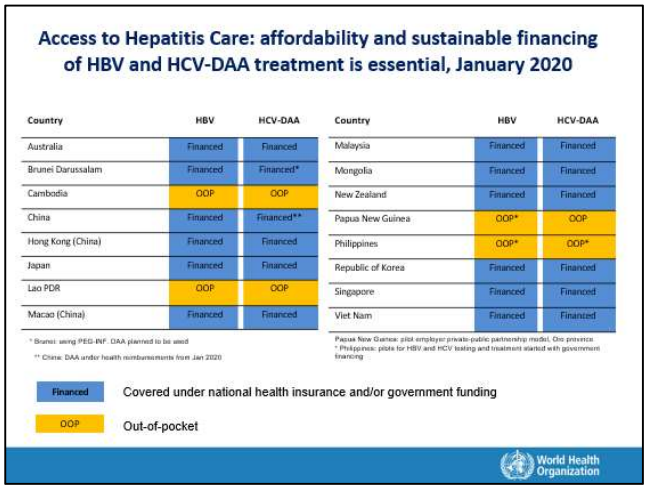
As an example, China's prices are US$ 10 per person-year for both tenofovir and entecavir, using generically manufactured medicines, and central procurement



Hepatitis C direct acting antiviral drugs (DAAs) are increasingly being registered in countries. New pangenotypic combination DAAs such as glecaprevir/pibrentasvir & sofosbuvir/velpatasvir/voxilaprevir is being registered in some countries but mainly high income.

Sofobuvir/daclastavir is registered in most countries, and is the most widely used pangenotypic regimen currently (as of Jan 2020).

Module 1C

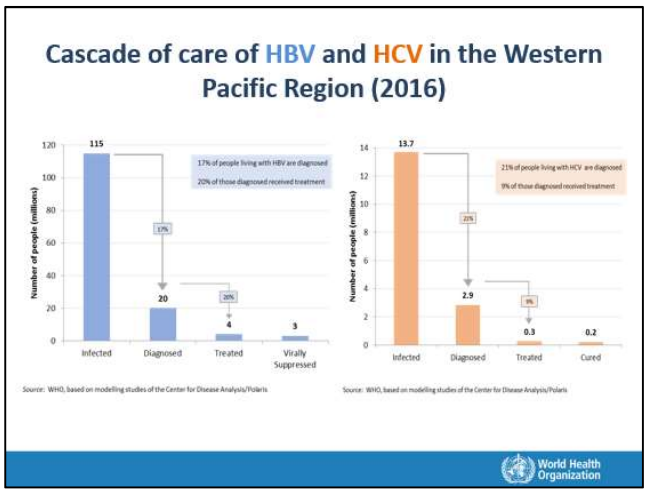


Access to medicines for HBV and HCV has seen improvements.
In general, most countries have drugs for hepatitis B registered, and most countries do have registration of DAA completed or in progress. However, registration of drugs does not mean access to most of the people who need it.

In several countries, hepatitis C drugs are now under universal health coverage (taken here as being financed under health insurance and thus, accessible to most of the population).

High costs for HCV DAAs remain challenging in the region even among countries which have the drug registered, and/or covered through health insurance
Affordability of tests and treatment remains an issue in many countries. Thus more work is needed for price reductions of tests and medicines.

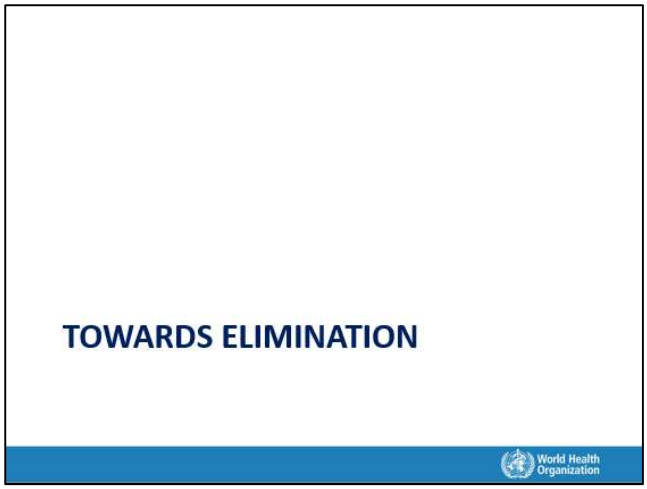
UHC: covered by health insurance and/or government financed
OOP: out of pocket



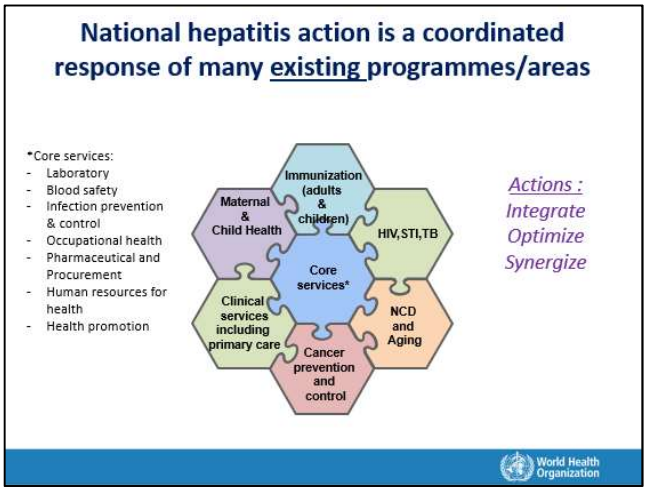
However, there is a large gap in care. Of those who are infected, only a minority know their status and are accessing treatment.

HBV cascade: not all people infected with HBV need treatment according to their disease staging.

Thus, much more needs to be done to scale up service delivery



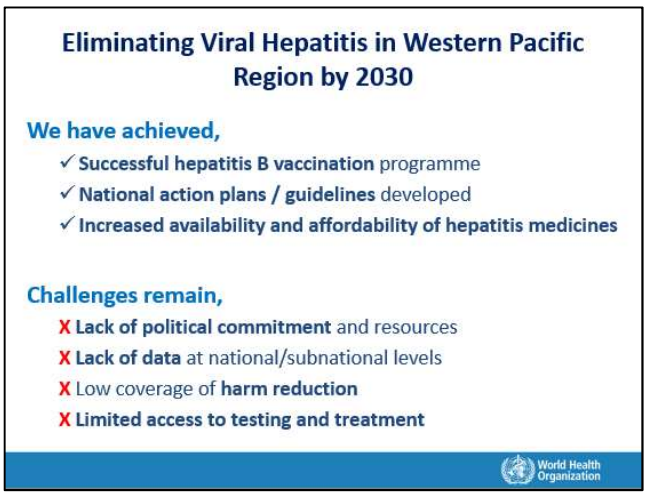
Module 1C



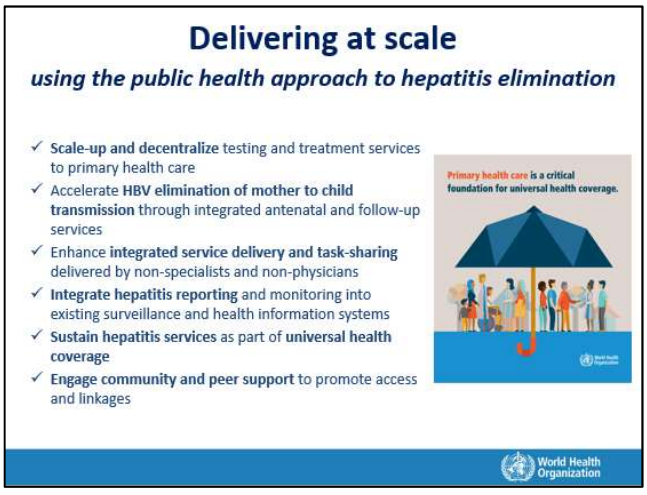
The learning from countries is that national comprehensive action is a coordinated response of many programmes and technical areas and is country-specific to the health systems, financing systems, current health reforms, approaches to access medicines, civil society, delivery systems etc.

All these programs/areas already exists.
The actions are to deliver integrated services, optimizing delivery of services, and synergizing common outcomes that programmes share:
Example 1: for the hepatitis B prevention of mother to child transmission – this requires at minimum the roles of immunization programmes, maternal child health to deliver prevention of mother to child transmission interventions and clinical services (physicians) to care for mother and child

Example 2: Treating chronic hepatitis B and C will reduce the risk of developing liver cancer. Thus, treating hepatitis early prevents liver cancer, and more can be done to advocate and communicate to the public in this area. Linking reporting of viral hepatitis and the cancer registry will help improve information



In the journey to elimination of hepatitis,



Summary

- Hepatitis is a major public health burden
- Prevention needs to be scaled up and sustained
- Chronic hepatitis B and C cause substantial health and related costs (economic burden, human suffering…)
  - Highly effective drugs available and high price still barrier in some countries
  - Treatment prevents progression of disease, lowers risk of developing liver cancer
  - HCV treatment (with new DAAs) : **CURE**
- Countries are overcoming barriers – much progress, but more needs to be done

World Health Organization

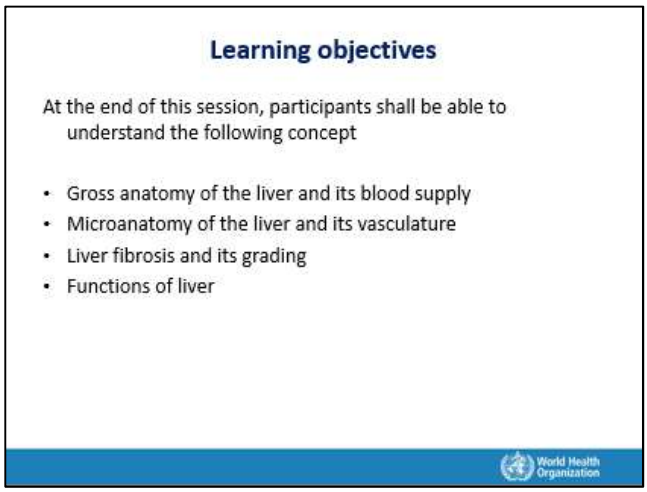
Thank You

World Health Organization

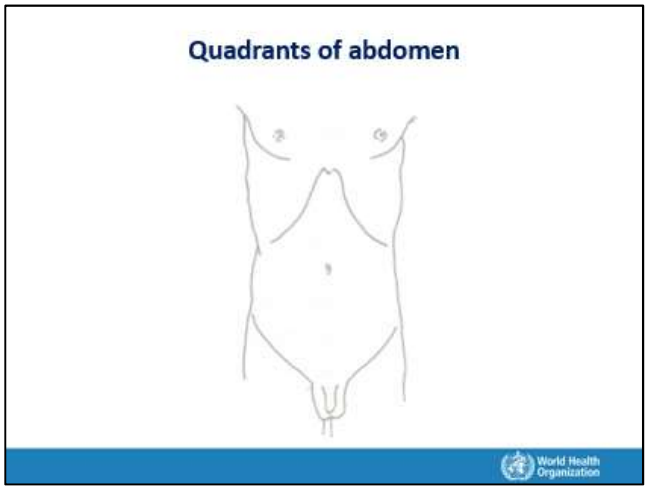
Module 2

Structure and function of the liver

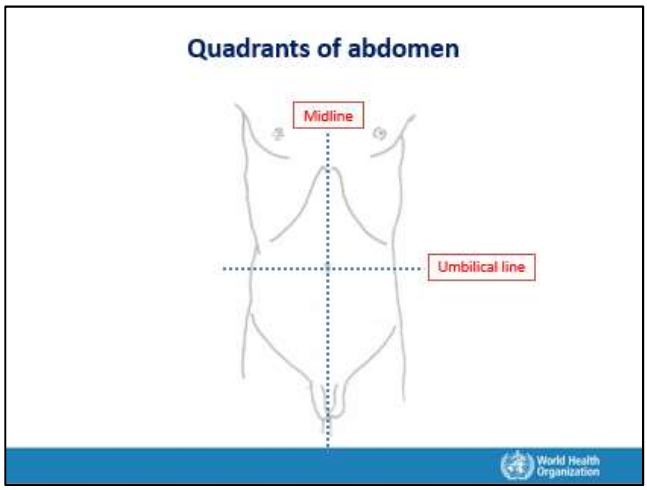
Module 2



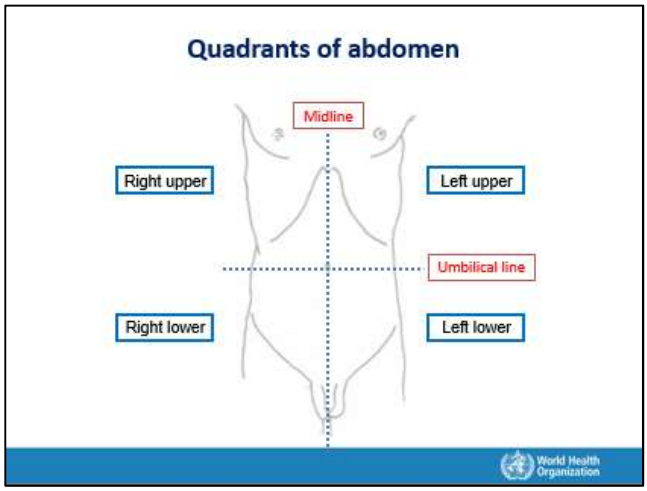
I welcome all the participants to this first session of the entire training programme. In this session, we will learn about the basics of the liver in terms of its anatomy, microscopic structure, and a few very important physiological functions that are most relevant in the context of viral hepatitis. We will also learn about acute and chronic liver injuries, and development of liver fibrosis in response to longstanding ongoing chronic injury such as chronic viral hepatitis. By the end of the session, we will be able to understand the pathological effect of liver injury and liver fibrosis on the human body.



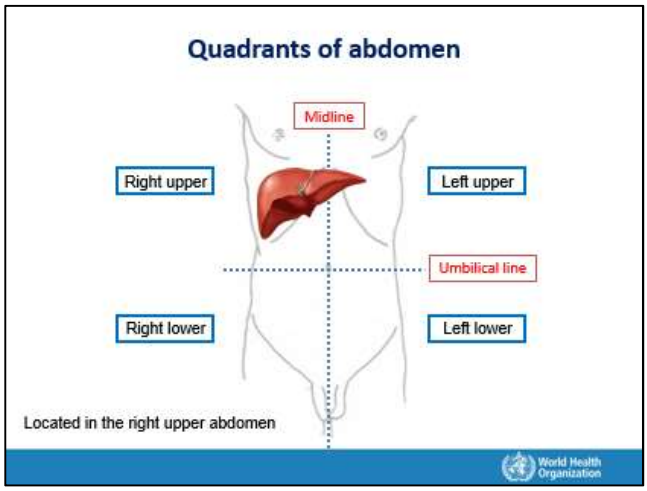
We all know that the abdomen extends vertically from the xiphisternum (above) to pelvic bone (below).



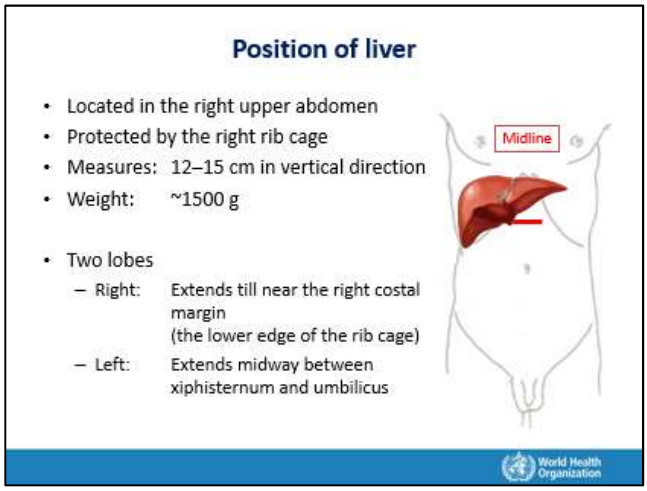
The entire abdomen is divided into four quadrants by a vertical line (from the xiphisternum to the pubic symphysis) and a horizontal line (drawn across the umbilicus).



The four quadrants of the abdomen are: right upper, right lower, left upper and left lower.

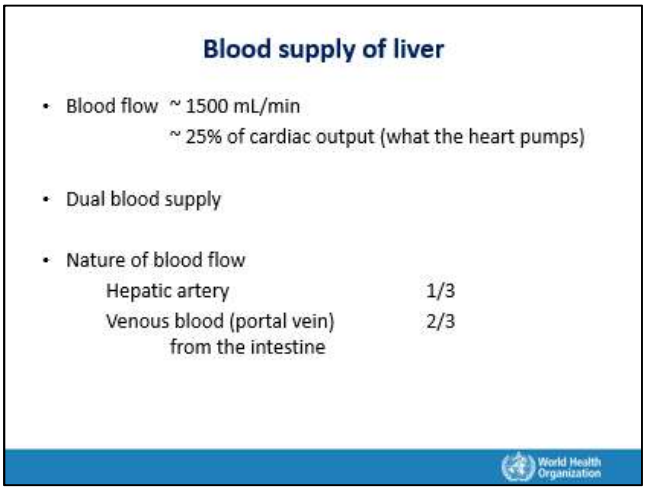


The liver is located in the right upper quadrant of the abdomen.



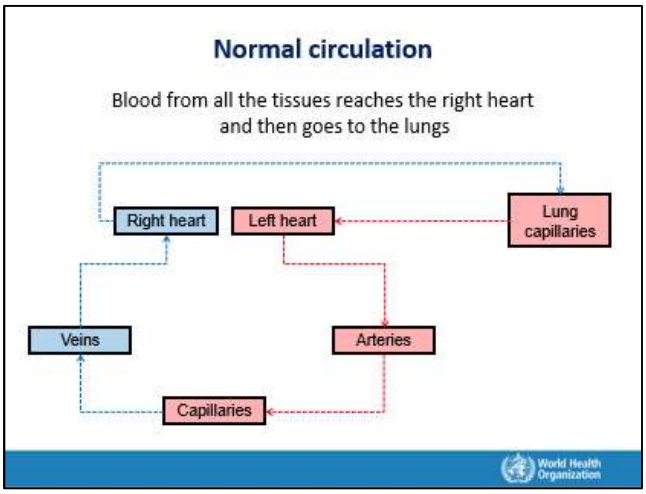
The liver is located deep in the right upper quadrant and is well protected by the right rib cage. Its size, as measured in the right midclavicular line, is about 12–15 cm and its weight is about 1500 g. The weight of the liver is approximately 2.5% of the body weight.

The right lobe of the healthy liver is not usually palpable. The left lobe may be palpable up to midway between the xiphisternum and umbilicus. This means that a palpable left lobe, in isolation, is not of clinical importance. In a patient, the consistency (normal consistency is firm), surface (normal is smooth, non-tender) and margins (normal is regular) of the liver are much more important features than the liver size alone.



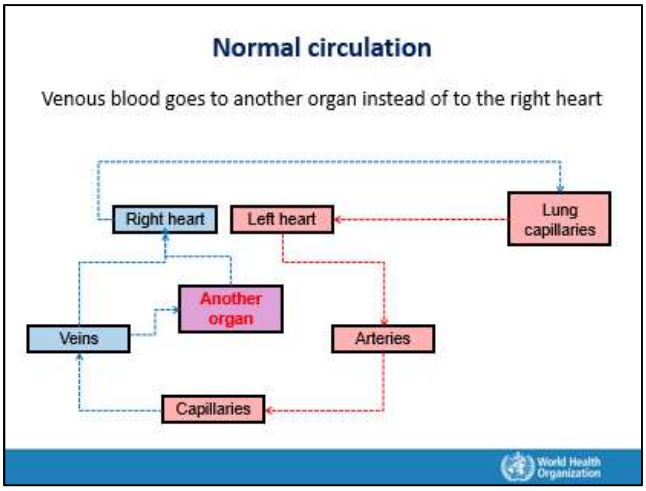
The liver is a very vascular organ. About 1500 mL of blood passes through the liver every minute, which is approximately 25% of the cardiac output (normal cardiac output is 5 L/min). Compared to its weight (which is about 2.5% of the body weight), it receives a massive blood supply.

It is important to realize that the majority (about 65%) of the blood supplied to the liver is deoxygenated venous blood (which carries much less oxygen than arterial blood) from the small and large intestine. Only one third of the supply is oxygenated arterial blood and carries a high level of oxygen. This dual blood supply serves three important functions. First, the dual blood supply gives a safety cushion to the liver and keeps it alive even if one supply is terminated because of some pathological state. Second, the venous blood carries several harmful substances, toxins and biological products derived from food and gut bacteria present in the large intestine; the liver acts as a filter that prevents the systemic circulation from exposure to these substances; when this filter function of the liver is impaired, such as in patients with liver failure, these harmful substances reach to the brain and the patient becomes unconscious. Third, venous blood carries a lot of nutrients from the small intestine; these nutrients, if released unchecked into the circulation, will produce metabolic imbalance. The liver acts as a temporary warehouse to store excessive amounts of these nutrients and releases them at the time of need (such as fasting).



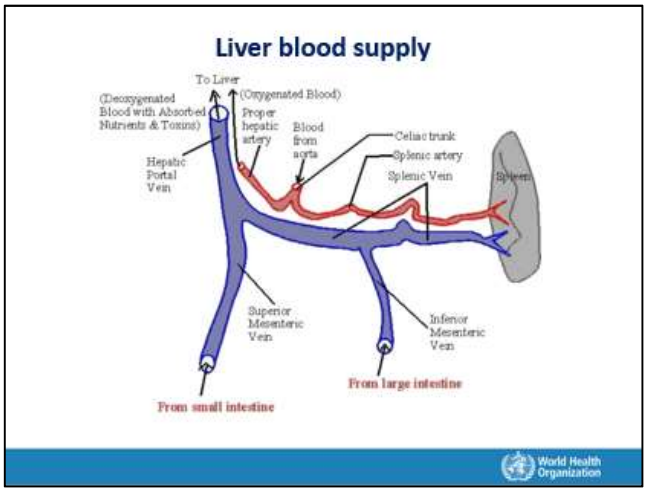
During normal blood circulation, deoxygenated blood is collected from all over the body by the venous system and is pumped by the right side of the heart into the lungs. In the lungs, oxygenation of blood takes place and oxygen-rich blood is returned to the left side of the heart and pumped through the arteries throughout the body.

Capillaries connect arteries to veins. Oxygen and carbon dioxide is exchanged in arteries, and blood collected from the capillaries returns to the lungs through veins.

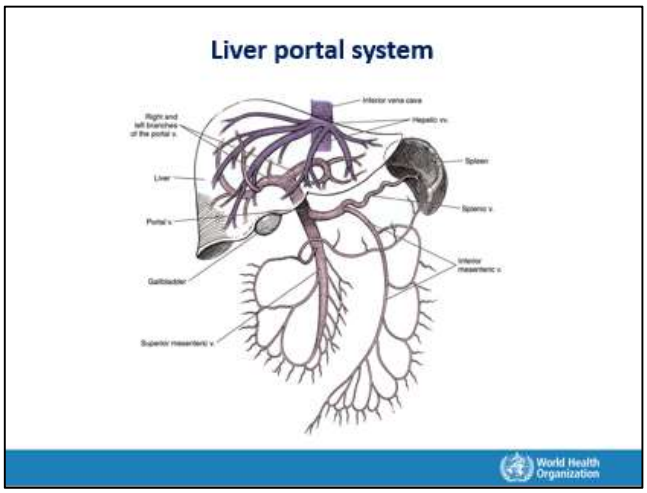


During normal blood circulation, deoxygenated blood is collected from all over the body by the venous system and is pumped by the right side of the heart into the lungs. In the lungs, oxygenation of blood takes place and oxygen-rich blood is returned to the left side of the heart and pumped through the arteries. During normal circulation, the blood collected from the capillaries is returned to the lungs through veins.

In the portal system, the blood returning from the capillaries is not directly returned to the venous system but is again passed through another set of capillaries in another organ or tissue. There are two portal systems in the human body: the pituitary–hypophyseal system in the brain and the second in the liver. The objective of this portal system is to provide the liver with extra circulation time and expose the blood to the extensive network of hepatocyte plates. It helps the liver to perform its metabolic and filtering activities more efficiently.



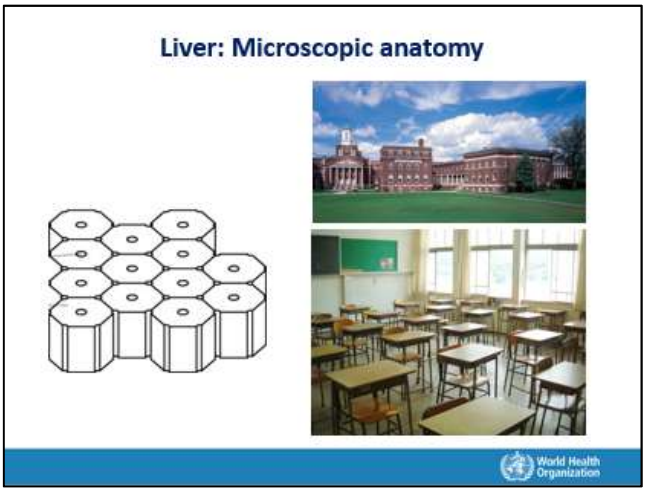
Almost all the blood coming from the intestine is collected and filtered through the liver.



This picture shows the venous drainage into the portal venous system and the venous drainage of the liver. The portal vein is formed by the superior mesenteric vein (which collect the nutrients and toxin-rich deoxygenated blood from the intestine) and splenic vein (which carries the immune-activated lymphocytes) from the spleen.

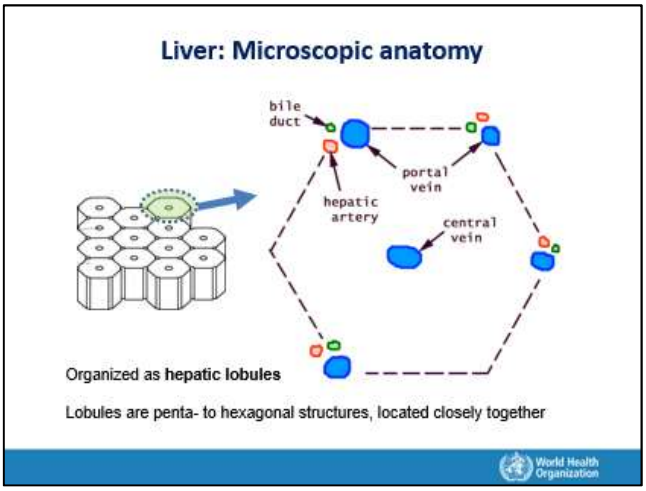
Inside the liver, the portal venous blood is first distributed to the extensive network of sinusoids and is then collected by three hepatic veins: right, middle and left hepatic veins. These hepatic veins drain into the inferior vena cava, which drains into the right side of the heart for oxygenation.

Now we will learn the microanatomy of the liver. We have to take out a piece of liver (liver biopsy) with the help of a Tru-Cut biopsy needle and examine it under the microscope. Liver biopsy is a risky procedure and needs hospitalization, skill to perform the biopsy, and a trained pathologist to interpret the findings under the microscope. It carries a finite, though small, risk of death following the procedure. Hence, these days, non-invasive methods are used to study the liver tissue, which we will learn during this course.

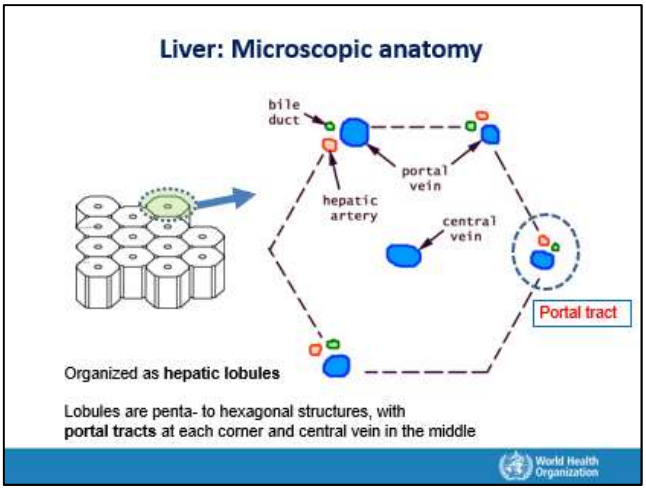


If we see the liver tissue under the microscope, we will find that the hepatocytes (liver parenchymal cells) are organized in **honeycomb**-like structures. These structure are called hepatic lobules. Such lobules are three-dimensional structures and are commonly hexagonal in shape.

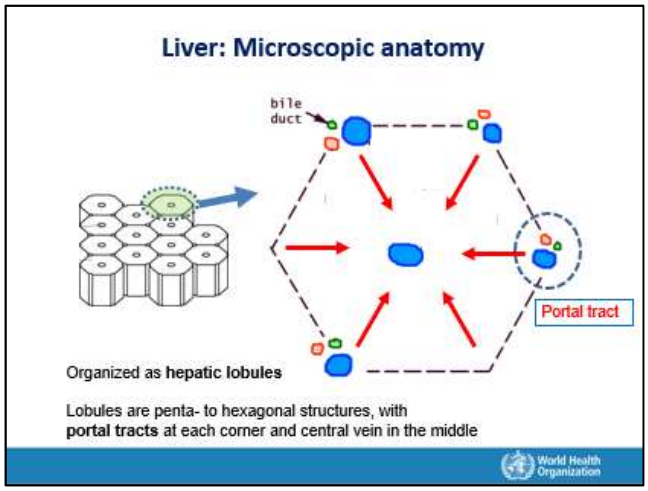
Within each lobule, the individual liver cells (hepatocytes) are well organized. We can compare the liver with a large school, liver lobule with a classroom, and each hepatocyte with every single chair inside the classroom. In a well-organized classroom, the chairs are organized in rows and placed at a definite distance, which facilitates easy movement of the students/teachers inside the classroom. Similarly, inside a liver lobule, hepatocytes are organized in the form of plates (akin to rows in a classroom), which are separated by sinusoids through which blood flows easily without much resistance.



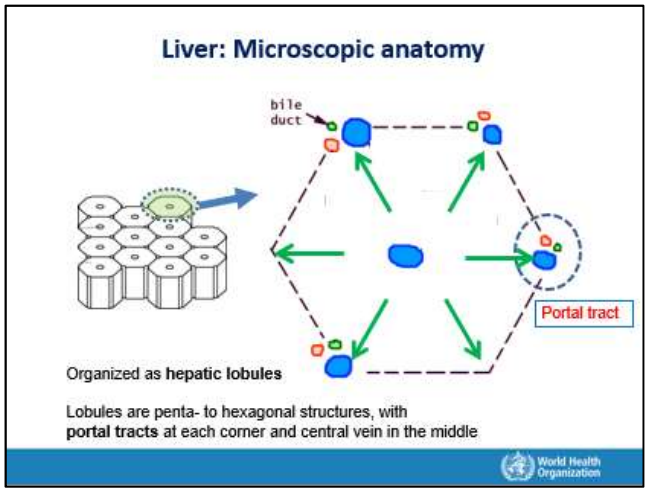
Each liver lobule has the following 3 structures in each corner of its hexagon: bile duct (green), portal vein (blue) and hepatic artery (pink). Usually there is one of each of these but sometimes there may be 2–4 bile ducts and sometimes only 2 structures. In the centre of each lobule there is one central vein (blue), which drains into the hepatic veins.



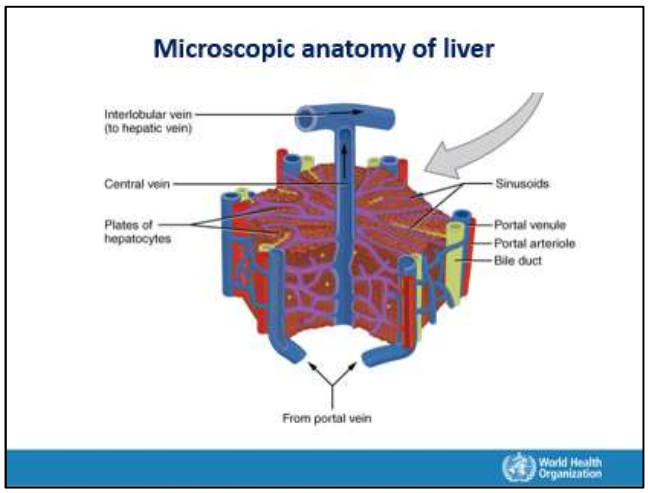
The three structures, along with the surrounding plate of hepatocytes, at the corner of the hepatic lobule are collectively called a **portal tract.**



In each lobule, blood from the branches of the portal vein and hepatic artery enters from the corner and flows in a centripetal direction to drain into the central vein. This flow of blood is slow and under low pressure, which gives adequate time for exchange of material between the blood and surrounding hepatocytes.



Bile is produced by hepatocytes. The bile produced by hepatocytes flows in a centrifugal direction (opposite to the flow of blood) to drain into a branch of the bile duct located in the corner of the lobule.



This is a three-dimensional picture of a hexagonal liver lobule. Each lobule is a three-dimensional structure, which shows the portal tract at each of the corner. Each portal tract has a branch of the portal vein (blue), hepatic artery (red) and bile duct (light green). The entire lobule is packed with hepatocytes organized in the form of plates (brown), which are separated by blood-filled sinusoids (purple).

Causes of liver injury

- The liver can be damaged by many insults **(separate talk)**
- Major causes
  - Infections, especially viruses
    - Hepatitis viruses – A to E
  - Non-infectious causes
    - Alcohol
    - Drugs
    - Non-alcoholic fatty liver disease

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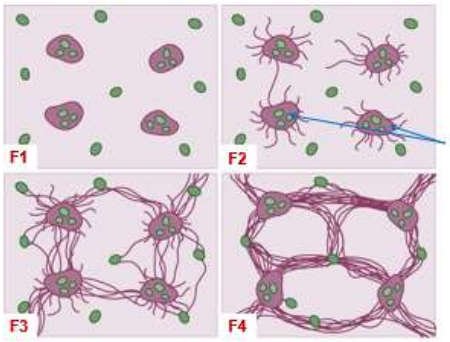
Till now we have learnt about the normal structure of the liver. The liver can be injured by any number of agents but the major causes are viral infections (hepatitis viruses such as hepatitis B or C), toxins (alcohol) or drugs (anti-tuberculosis drugs such as INH, rifampicin, pyrazinamide; antiepileptic drugs – phenytoin; paracetamol; oral contraceptive pills, etc.).

Prolonged liver injury leads to scarring (fibrosis)



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Fibrosis starts around the portal area and extends gradually into the lobular parenchyma. There are four grades of fibrosis: F1, F2, F3, F4.

Response of the liver to injury

- Acute (short-term) injury
  - Inflammation
  - Swelling and mild enlargement
  - Death of cells and impairment of liver function
- Chronic (long-term) injury
  - Chronic inflammation
  - Fibrosis (scarring)

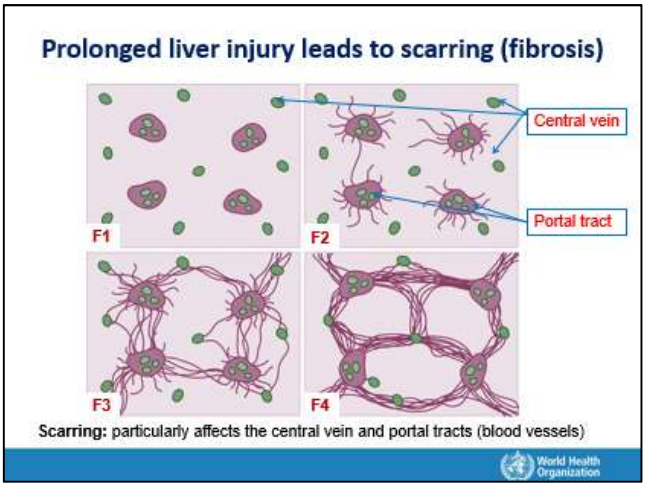
World Health Organization

Regardless of the cause, liver injury manifests in form of hepatitis which means inflammation of the liver. There are five components of inflammation. What are these? (The 5 components are: rubor – redness, calor – heat, dolor – pain, tumor – swelling, and loss of function).

Liver inflammation (or hepatitis) could be either acute or chronic.

Acute hepatitis is characterized by sudden and massive death of hepatocytes over a short period of time and is characterized by all the five components of inflammation. Clinically we find liver enlargement (tumor); tenderness on palpation (dolor); jaundice with or without coagulopathy/encephalopathy (loss of function).

In contrast, chronic hepatitis is caused by slow but long-standing injury, which leads to an ongoing process of cell death and healing. Healing during chronic hepatitis is see as fibrosis.

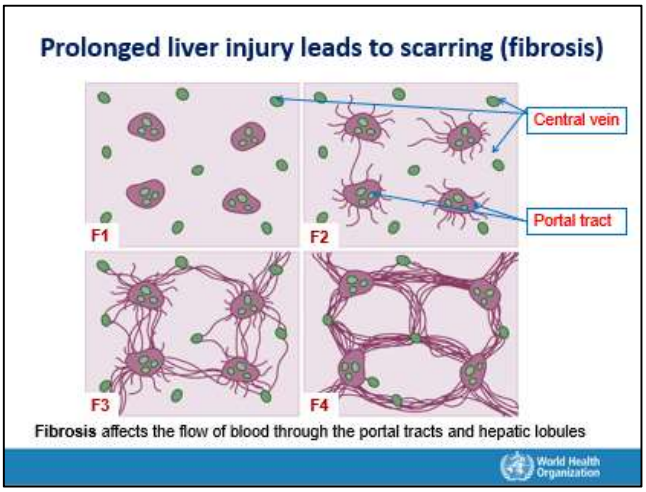


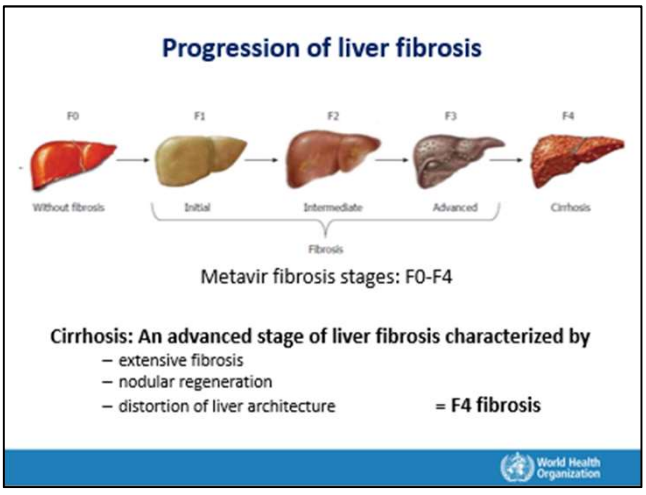
F1 indicates fibrosis in the portal area; the fibrosis has not extended beyond the limiting plate of the portal tract.

F2 indicates portal fibrosis with fibrous septae; thin septae are developing, which have started extending from the portal tract to the liver parenchyma; very few **thin** septae might be seen joining two adjacent portal tracts.

F3 indicates numerous septae without cirrhotic nodules; a number of **thick** fibrous bands can be seen connecting adjacent portal tracts, which convert each liver lobule into a single nodule surrounded by a thick fibrous band; there will be no or very few **thin** bands from the portal tract to the central vein.

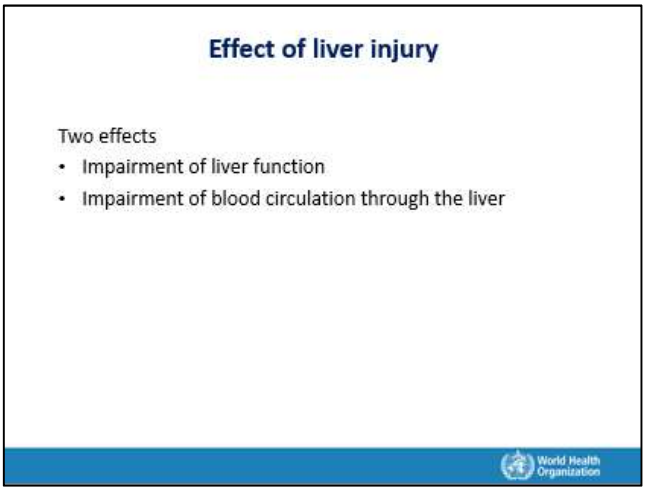
F4 indicates cirrhosis, nodule formation or findings suggestive of nodule formation; there will be a number of thick bands extending from the portal tract to both adjacent portal tracts as well as the central veins. Hence, the entire lever lobule is converted into a clump of multiple smaller nodules each surrounded by thick fibrous septae.



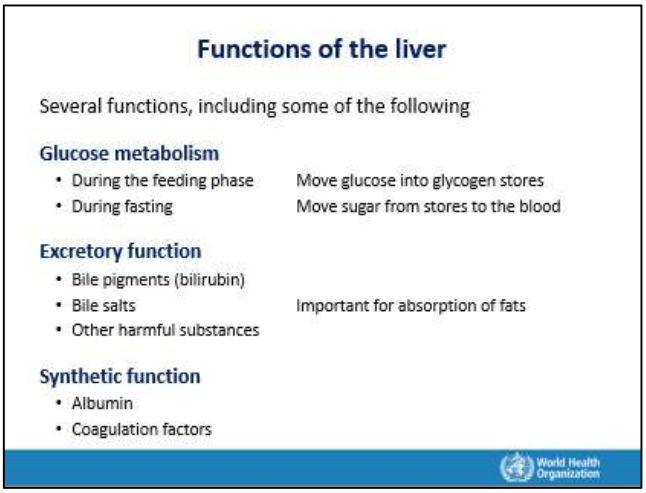


The spectrum of liver disease ranges from minimal fibrosis to cirrhosis. Without antiviral therapy, chronic hepatitis gradually progresses to cirrhosis in 20–30 years. The Metavir fibrosis staging system is a scoring system for assessing liver fibrosis based on pathological findings. F4 Metavir fibrosis stage is also known as cirrhosis.

Distortion of the architecture of the liver lobule leads to hindrance in blood flow, just as the difficulty caused in trying to move about in a classroom with disorganized chairs. The fibrosis converts the non-turbulent, low-pressure blood flow in the lobule sinusoids into a turbulent high-pressure flow. This stage is known as portal hypertension.



As a part of the inflammation of liver injury, there are two types of adverse effects: impairment of liver function and impairment of blood circulation through its parenchyma.



There are three major functions of the liver: (i) glucose metabolism, which maintains the blood glucose within an acceptable range; (ii) excretion of waste substances from the body in the bile; and (iii) synthesis of important body proteins such as albumin and coagulation factors. Role of albumin: maintains the oncotic pressure; the half-life is 21 days, which is important to know in cases of liver dysfunction.

Liver disease: Effect on liver function

Several functions, including some of the following

Glucose metabolism

- During the feeding phase — Blood sugar too high (hyperglycaemia)
- During fasting — Blood sugar too low (hypoglycaemia)

Excretory function

- Bile pigments (bilirubin) — Jaundice
- Bile salts — Poor absorption of fats
- Other harmful substances — Unconsciousness

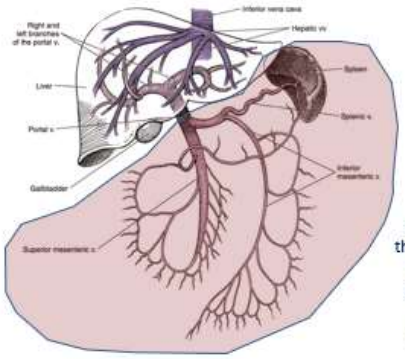
Synthetic function

- Albumin — Edema, (ascites)
- Coagulation factors — Deranged coagulation, bleeding

World Health Organization

Impaired glucose metabolism results in postprandial hyperglycaemia and post-fasting hypoglycaemia. Impaired excretion of bilirubin results in jaundice. Impaired clearance of toxic wastes may lead to unconsciousness. Albumin is the main protein that maintains the oncotic pressure and maintains the body vascular volume. If albumin is not synthesized then fluid will move out from the blood vessels to the third spaces such as the peritoneal cavity and pleural cavities. It results in ascites and pleural effusion. Impaired synthesis of coagulation factors will lead to bleeding manifestations.

Effect of cirrhosis on liver circulation



Decreased blood flow through the liver leads to high pressure in the portal venous system or **portal hypertension**

World Health Organization

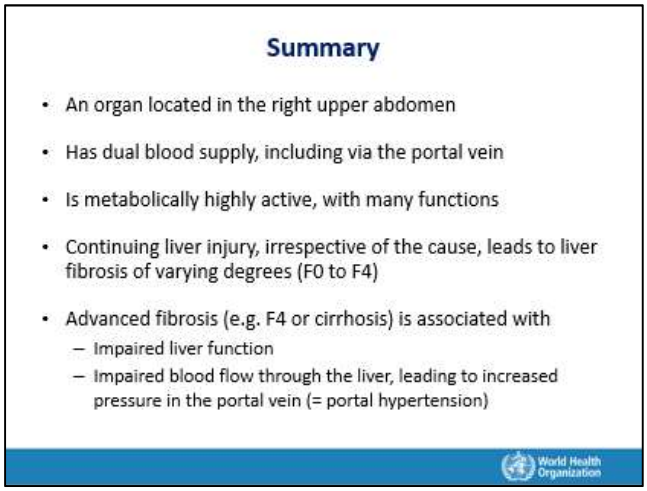
Blood vessels proximal to the liver get congested, which is known as portal hypertension.

Liver disease: Effect on blood circulation

- Obstruction of blood flow through the hepatic lobules leads to increased pressure in the portal vein
- Portal hypertension = increased pressure in the portal vein
- Manifestations
  - Development of collateral veins (varices) — Abnormally enlarged veins
  - Exudation of fluid into abdomen — Ascites
  - Congestion of venous system — Splenomegaly >pancytopenia

World Health Organization

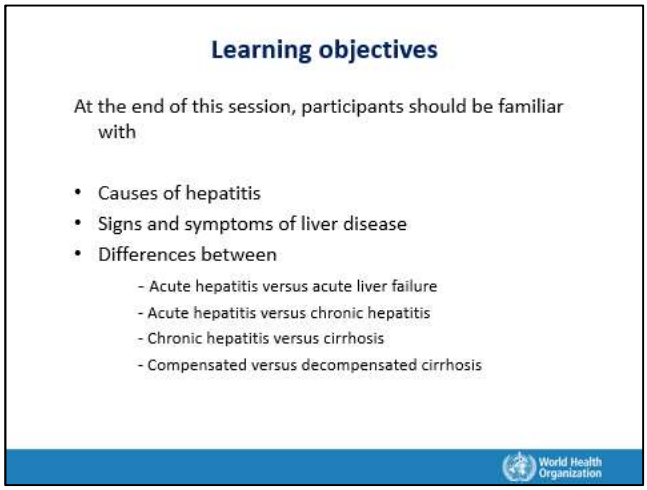
Portal hypertension results in congestive splenomegaly, ascites, and formation of collaterals at various places. The newly formed collateral vessels manifest as esophageal varices or gastric varices. Hypersplenism results in pancytopenia, in particular, thrombocytopenia.



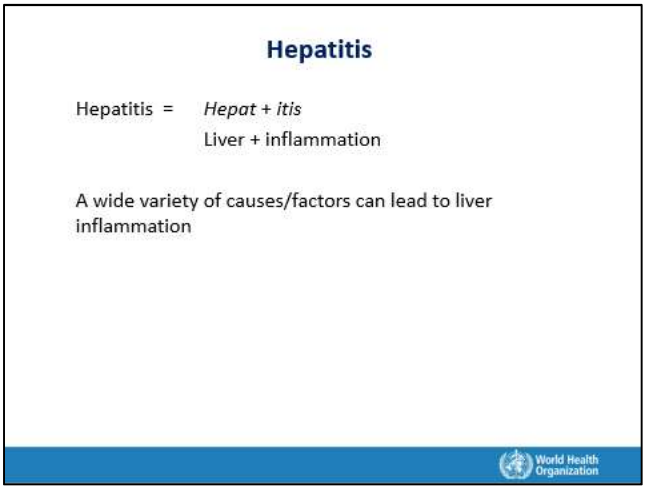
In summary, the liver is a highly metabolically active organ located in the right upper quandrant of the abdomen. It has a dual blood supply. Chronic liver injury results in liver fibrosis, which could range from F1 to F4 or cirrhosis. Fibrosis results in portal hypertension.

Module 3

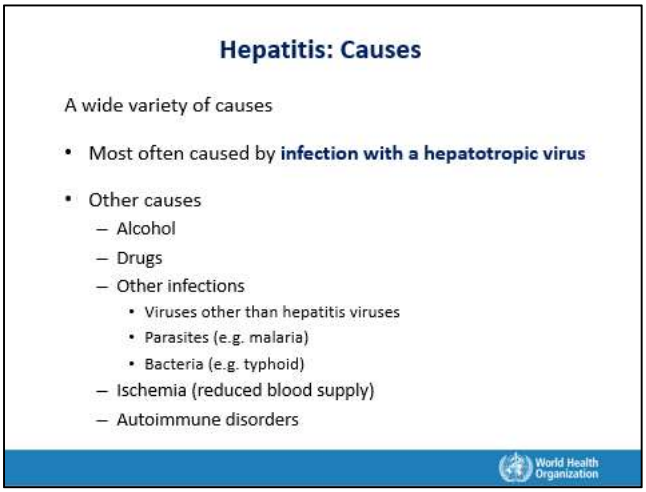
Causes and symptoms and signs of liver injury



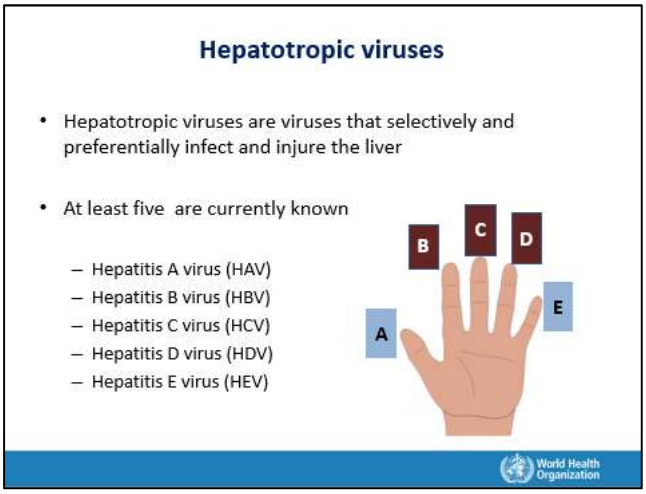
In this session we will learn about the causes of hepatitis, its signs and symptoms, and features that helps us in differentiating between the various clinical syndromes and stages of viral hepatitis.



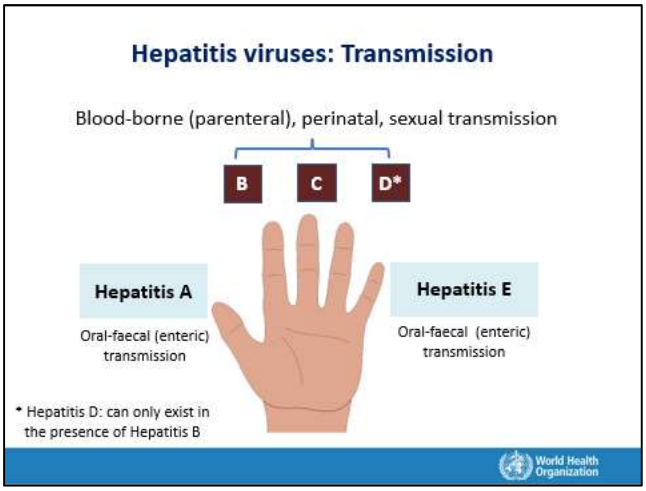
Hepatitis means inflammation of the liver, which could be caused by a range of agents.



The liver can be injured by any number of agents but the major causes are viral infections (hepatitis viruses such as hepatitis C or B), toxins (alcohol) or drugs (antitubercular drugs – INH, rifampicin, pyrazinamide; antiepileptic drugs – phenytoin; paracetamol overdosing; etc.).



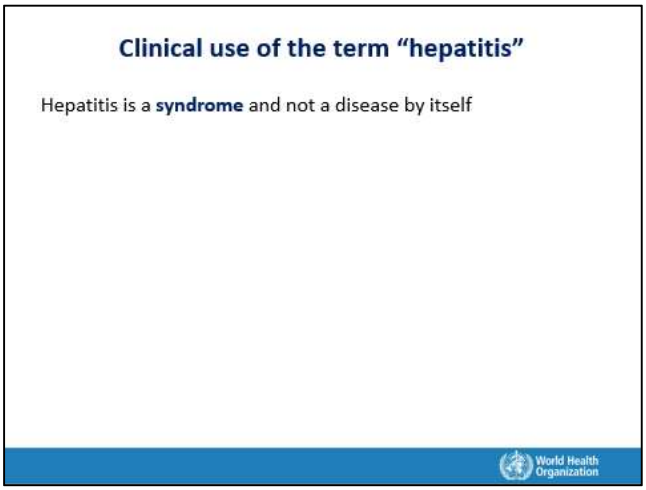
Viral hepatitis is most commonly caused by hepatotropic viruses. Hepatotropic viruses are so named because the liver is the primary site of infection for these viruses. These viruses may have limited involvement of the extrahepatic organs through an indirect mechanism. Further, several non-hepatotropic viruses could also cause hepatitis such as dengue, cytomegalovirus, herpesvirus, varicella, etc. There are five known hepatotropic viruses: HAV, HBV, HCV, HDV and HEV.



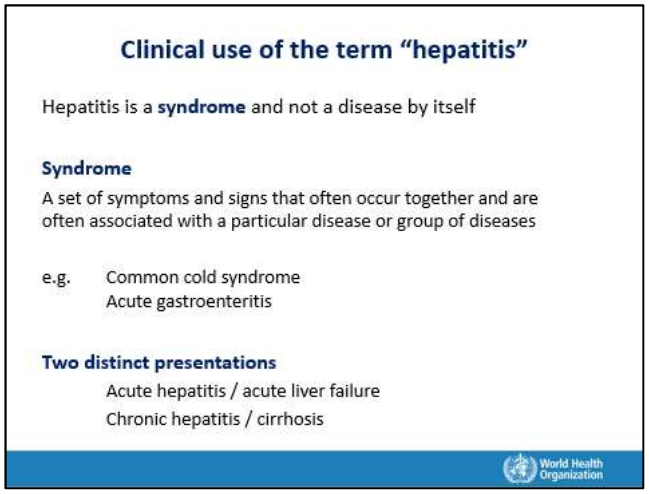
The five hepatotropic virus could be clubbed into two groups based upon certain similarities among them:

(A) enterically transmitted viruses, which include HAV and HEV. HAV primarily affects children whereas HEV primarily affects adults; both these viruses cause acute hepatitis, which recovers completely without causing any longstanding chronic hepatitis. HEV can occasionally cause chronic hepatitis in the immunocompromised population, in particular, in European countries; HAV is not reported to cause chronic hepatitis.

(B) parenterally transmitted viruses, which include HBV, HDV and HCV. The most common parenteral routes of transmission include transfusion of contaminated blood, use of unsafe injections or needles, transmission from a pregnant woman to her baby, and unsafe sex.

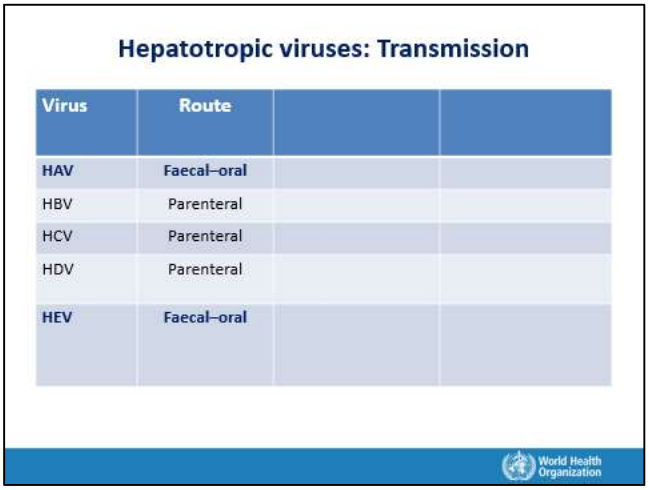


Hepatitis is a syndrome and not a disease. A syndrome is characterized by a group of signs and symptoms that could have several causes. Here, hepatitis syndrome is characterized by prodromal symptoms, jaundice, raised liver enzymes, hepatomegaly, among other symptoms, regardless of the virus that has caused it.

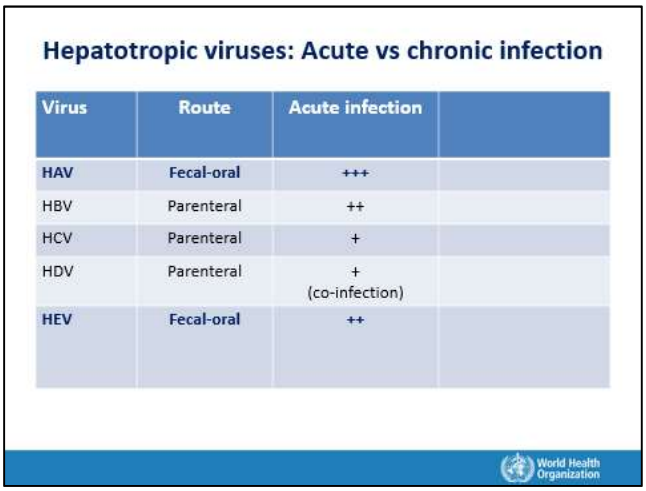


In an analogy, we can compare hepatitis to pneumonia, which is also a syndrome and could be caused by any number of pathogens; similarly, in the surgical area, bowel obstruction is a syndrome characterized by pain abdomen and vomiting but it could have several causes such as tuberculosis, malrotation, stricture, etc.

Hepatotropic viruses could have two syndromic presentations: first, acute hepatitis, which could occasionally progress to acute liver failure; and chronic hepatitis, which could progress to liver cirrhosis.



This table summarizes the routes of transmission and the clinical syndrome caused by the two groups of hepatotropic viruses.

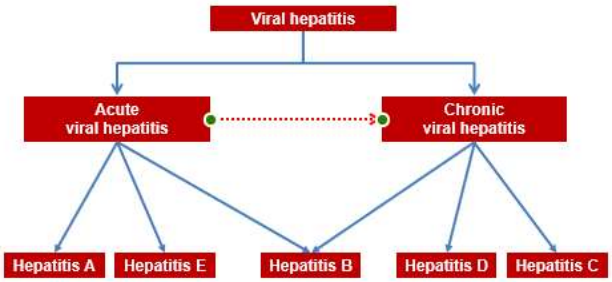


Hepatotropic viruses: Acute vs chronic infection

Virus	Route	Acute infection	Chronic infection
HAV	**Faecal–oral**	**+++**	**No**
HBV	Parenteral	++	+++
HCV	Parenteral	+	+++
HDV	Parenteral	+ (coinfection)	++ (superinfection)
HEV	**Faecal–oral**	**++**	**No, (except in a few immunosuppressed persons)**

World Health Organization

Common presentations of viral hepatitis



World Health Organization

Please note a small difference here from what we have learned so far. HBV can cause acute hepatitis as well as chronic hepatitis. This is because the syndromic presentation of HBV infection is determined by the age of the host at which virus exposure occurred.

Among children, HBV infection frequently progresses to chronic hepatitis whereas in adults it presents as acute hepatitis. We will learn more about it in due course.

Acute hepatitis

World Health Organization

Acute viral hepatitis

- Inflammation of the liver due to a recent infection with a hepatotropic virus
- Usually short duration (days to weeks)

World Health Organization

Acute hepatitis implies a recently acquired infection. Acute hepatitis is marked by sudden and massive death of the hepatocytes over a short period of time and is characterized by all the five components of inflammation. Clinically we find liver enlargement (tumor); tenderness on palpation (dolor); jaundice with or without coagulopathy/encephalopathy (loss of function).

Acute viral hepatitis

- Three phases: Prodrome, Icteric phase, Convalescence
- Prodrome
  - Non-specific symptoms (malaise, fever, fatigue, vomiting, aversion to food, sometimes rash, joint pains, itching)
  - Lasts a few days
- Icteric phase
  - Jaundice (yellow eyes/skin), dark urine, light-coloured stools
  - Lasts days to weeks
- Convalescence
  - Gradual recovery over a few days to weeks

World Health Organization

Typically, acute viral hepatitis has three phases: prodromal, icteric and convalescent. The prodromal phase consists of a variable mixture of marked anorexia, fever, generalized body ache, joint pains, headache, myalgia, malaise, nausea and vomiting. A few patients may also have skin rash or lymphadenopathy. Anorexia is often the most remarkable symptom. This phase usually lasts for 5–7 days and ends with the onset of jaundice. During the prodrome, serum transaminases are elevated, with their level usually exceeding 3 times the upper limit of normal (ULN) and often being >10-fold. In all forms of viral hepatitis, this phase is associated with the potential for transmission of infection and the viruses can be detected in various body fluids, depending upon the particular agent.

The icteric phase is marked by clinical jaundice. It usually lasts a few (often 2–4 but longer at times) weeks, and is followed by lowering of serum bilirubin. Abdominal examination reveals mid- and right upper quadrant tenderness, mild tender hepatomegaly, and occasionally mild splenomegaly and mild ascites.

In the convalescent phase, jaundice recedes, all other symptoms improve and organomegaly regresses. Some cases with acute viral hepatitis, particularly those due to HAV and HEV infection, may have a prolonged phase of cholestasis with intractable pruritus, that may continue for few months.

Differential diagnosis of acute viral hepatitis

- Many other diseases can have symptoms similar to acute viral hepatitis
- Systemic infections
  - Malaria
  - Dengue
  - Leptospirosis
- Drug-induced liver injury
- Biliary obstruction

World Health Organization

In tropical countries, where systemic infections are much more common, we need to differentiate these from acute viral hepatitis. It is very important because most of these infections as well as viral hepatitis occur during the same period of the year and a few of them have specific and effective treatment.

Further, drug use is very common in developing countries, in particular, antitubercular drugs, which could cause drug-induced liver injury (DILI) and will need timely identification and drug discontinuation.
Similarly, obstructive jaundice is also common and needs to be identified.

Examination

- Jaundice of variable degree
- Slight enlargement of the liver, usually soft, may be mildly tender
- No or mild splenomegaly
- No abdominal mass
- No ascites (in some, mild ascites may be present)

World Health Organization

Acute hepatitis is characterized by soft, mildly tender hepatomegaly; normal-size spleen or mild, soft, non-tender splenomegaly; no ascites or presence of mild ascites in occasional patients.

Indicators of acute viral hepatitis in a jaundiced patient

- Prodromal features, especially loss of appetite
- Seasonal occurrence
- Epidemiological setting – outbreak
- Presence of risk factors
- Relatively minor nature of fever, abdominal pain, etc.
- Sudden onset of conjugated hyperbilirubinaemia
- Marked elevation of ALT/AST (usually >10-fold upper limit; often much more, even up to 150 times)

Note: Do not forget to ask about intake of hepatoxic drugs

World Health Organization

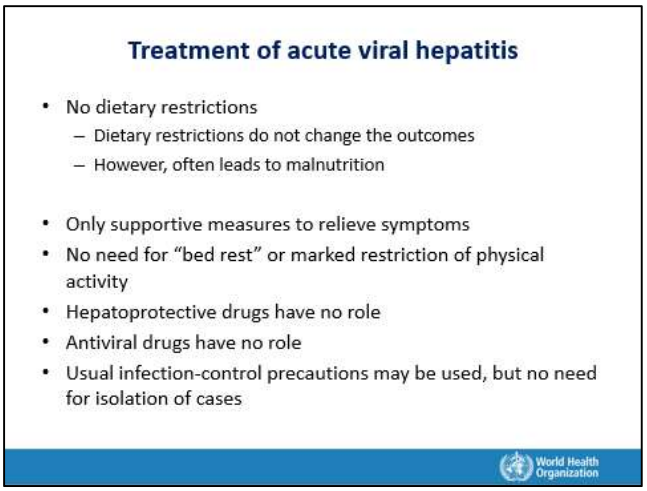
Marked loss of appetite is the most prominent prodromal feature. It is known that during viral hepatitis, smokers develop an aversion to smoking as well. Cases caused by the waterborne hepatotropic viruses (HAV and HEV) predominantly occur during either the hot summer months (because of scarcity of safe drinking water and poor hygiene) or in the post rainy season, when the risk of faecal contamination of drinking water is the maximum.
During travel, the risk of exposure to contaminated food and water is increased, which could transmit HEV/HAV. Because their median incubation period is usually in the range of 4–8 weeks, we should ask for the history 1–2 months before the onset of symptoms.

Investigations

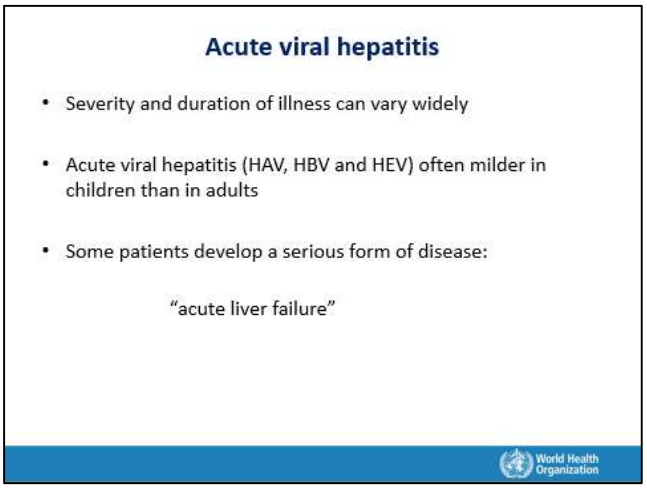
- Liver function tests
  - Serum bilirubin
  - Liver enzymes: ALT, AST, Alkaline phosphatase
  - Prothrombin time (INR)
- Viral serology
  - IgM anti-HAV
  - IgM anti-HEV
  - HBsAg -> IgM anti-HBc
  - Anti-HCV and/or HCV RNA
- Ultrasound may help to distinguish from biliary obstruction

World Health Organization

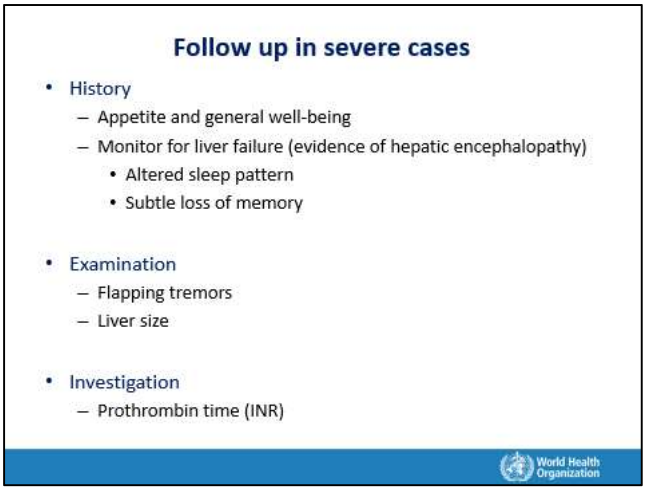
During the laboratory work-up of acute hepatitis, we need to have liver function tests; prothrombin time with INR; ultrasound (USG) abdomen if biliary obstruction or other pathology such as liver abscess is suspected. To diagnose if hepatitis virus are the cause of acute hepatitis, we need IgM testing for HAV, HEV and screening for HbsAg and anti-HCV. If HBsAg is positive, then IgM anti-HBc should be done to confirm. If anti-HBc IgM is positive, this could be acute HBV or flare up of chronic HBV infection. In the early phase of acute HCV, anti-HCV may be negative, thus, HCV RNA is the optimal test. Patients who are acutely infected with hepatitis C virus typically develop abnormal laboratory findings in the following order: detectable HCV RNA, followed by elevation in ALT, and then HCV antibody.



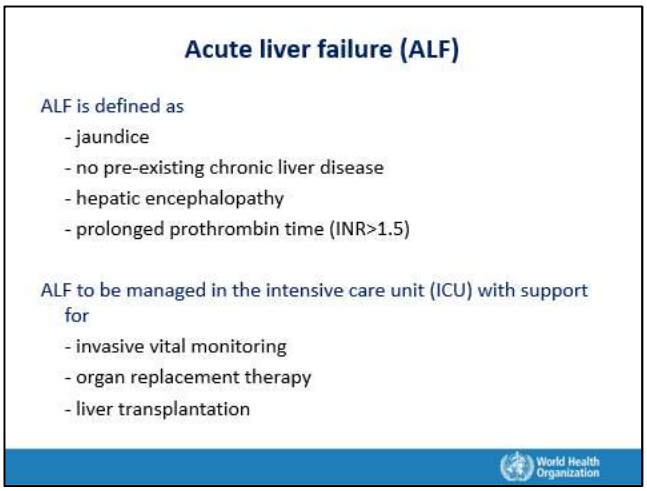
Most patients with acute viral hepatitis improve with supportive symptomatic treatment, and specific medical treatment is neither indicated nor available. Dietary restrictions and enforced bed rest have NO role in the treatment of acute viral hepatitis. The former merely serves to undermine the patient's nutritional status. There is no specific therapy for acute HAV and HEV. Acute HBV does not need any therapy though some data suggest that antiviral drugs may be useful in patients with severe acute viral hepatitis or acute liver failure due to HBV infection.



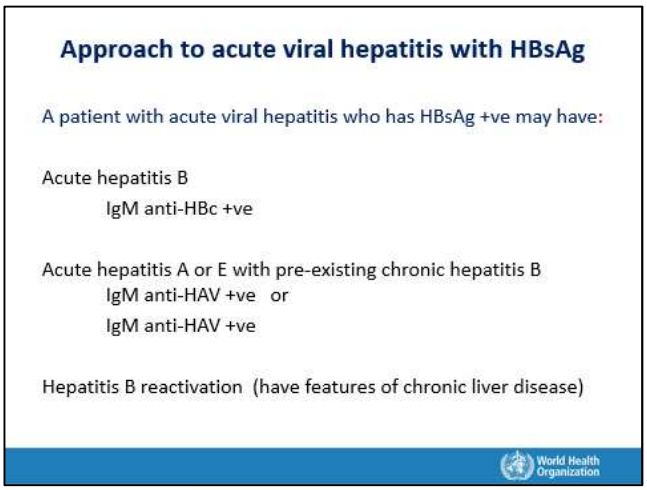
The severity of illness due to acute viral hepatitis is very variable. In general, it is milder among children than adults. The reason for this difference in disease severity is not well understood. Very occasionally, patients with acute viral hepatitis may progress to acute liver failure.



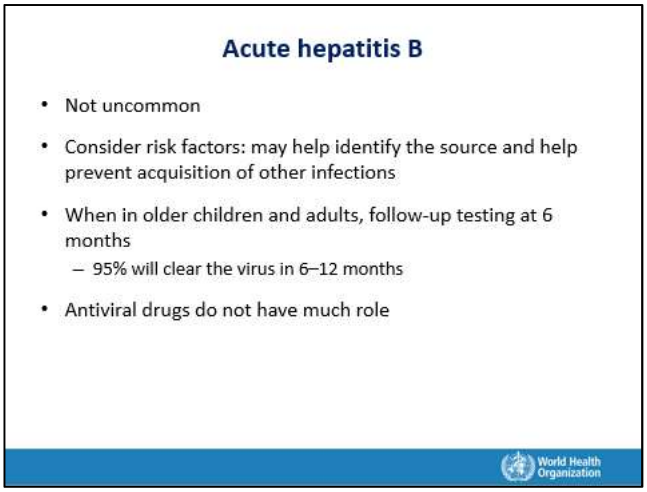
Patients with acute viral hepatitis are at risk, though very small, of progression to acute liver failure. Hence, all acute hepatitis patients should be monitored for the early features of acute liver failure. On clinical examination, presence of an altered sleep pattern and flapping tremors are the early signs of liver failure. The only laboratory test that indicates liver failure is prothrombin time (International Normalized Ratio, INR). Hence, during follow up for acute viral hepatitis, INR must be repeated as and when required.



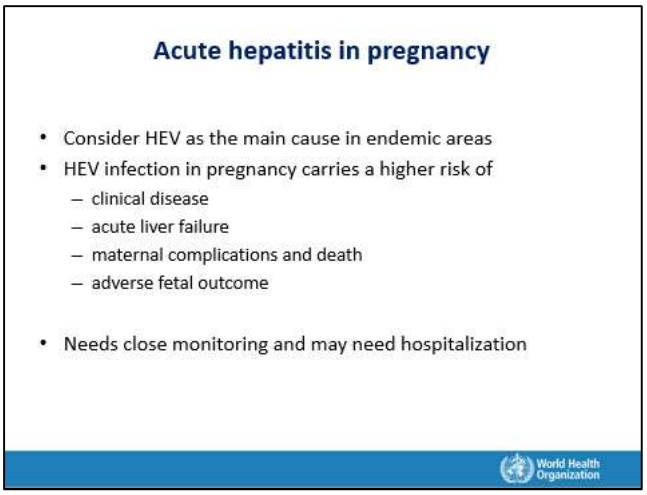
Acute liver failure is characterized by additional features of hepatic encephalopathy and prolonged INR. Though there is no specific drug treatment for ALF, early detection is useful so that the patient can be shifted early to an intensive care unit where an organ support system may be in place and liver transplantation, if needed, could be done.



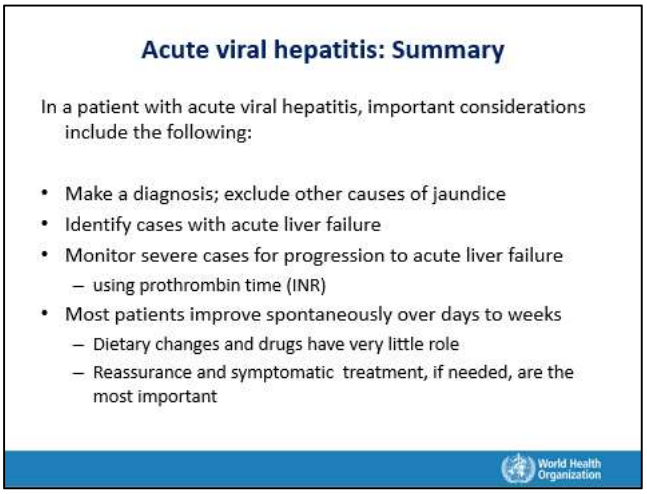
Sometimes patients with chronic HBV infection may present with acute viral hepatitis-like features. This happens because of the HBV virus reactivation. HBV reactivation could be suspected in the presence of radiological or laboratory markers of chronic liver disease, cirrhosis or portal hypertension.

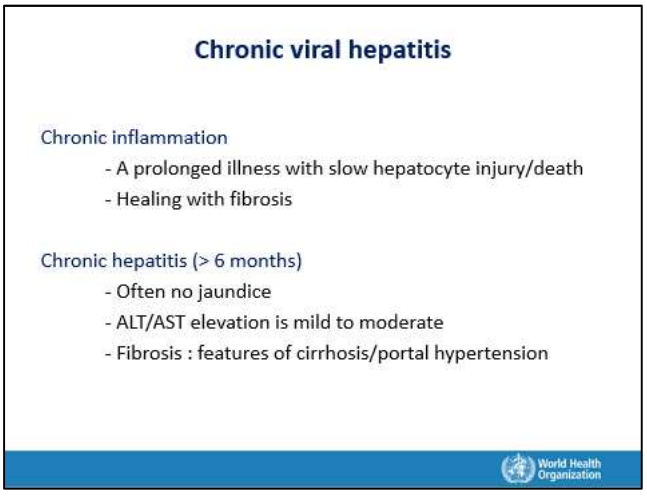


HBV has a unique pattern of clinical illness, which is primarily determined by the age of the host at the time of exposure. There is an inverse relationship between the risk of developing acute hepatitis and its progression to chronic infection and the age of the host. Infections during infancy remain asymptomatic and carry more than 90% chance of progressing to chronic infection. Up to the age of 5 years, about 20% develop chronic infection. After the age of 5 years and particularly in adults, more than 90% develop acute hepatitis (usually mild symptoms, with some people having severe symptoms). Most adults clear the virus within six months and recover fully.

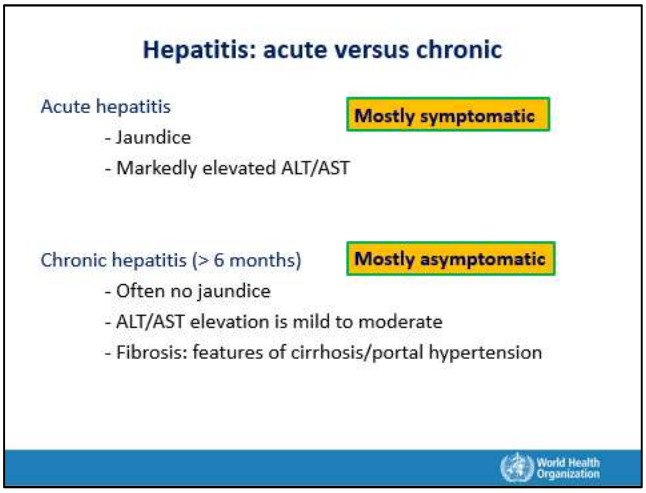


Pregnant women, in particular those in their third trimester of gestation, are prone to developing acute HEV infection. Acute HEV in pregnant women frequently develop acute liver failure (about 20–25%) with high rates of maternal and fetal mortality.

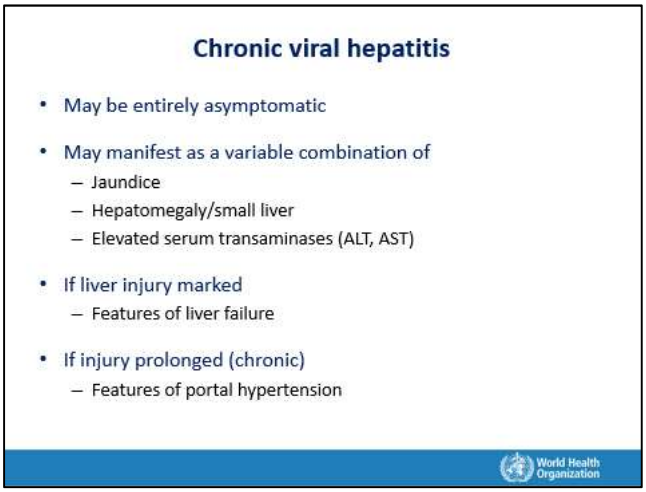




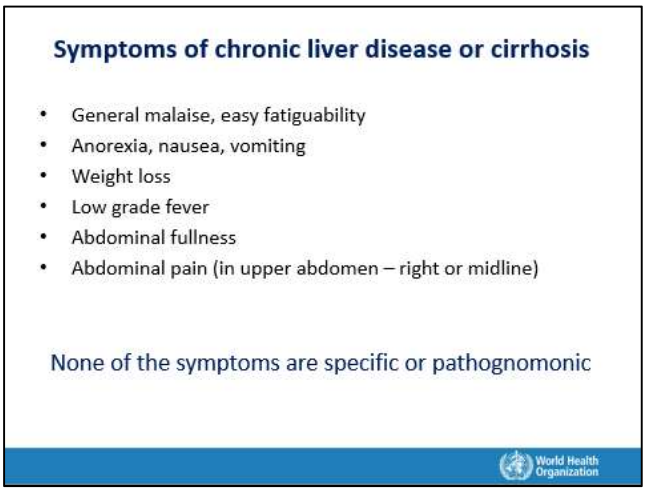
Chronic hepatitis is characterized by slow but longstanding injury, which leads to an ongoing process of cell death and healing. Healing in chronic hepatitis is in the form of fibrosis. Conventionally, if hepatitis continues for >6 months, it is labelled as chronic hepatitis. In contrast to acute viral hepatitis, chronic hepatitis is characterized by absence of jaundice, mild-to-moderate elevation of serum levels of liver enzymes, with or without features of cirrhosis or portal hypertension.



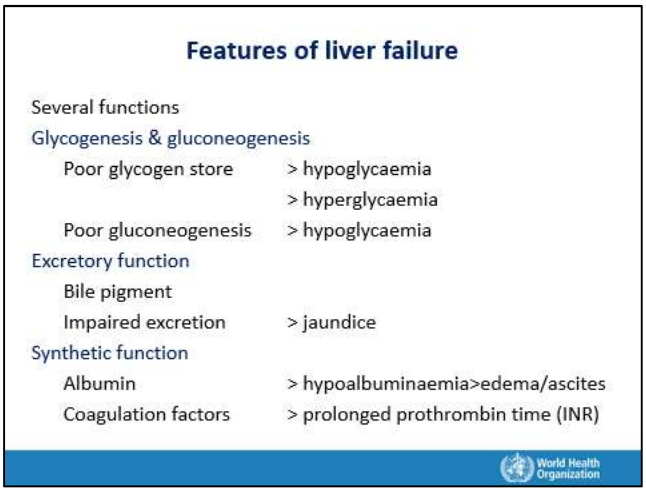
Because of prodromal symptoms and clinical jaundice, patients with acute hepatitis come to the physician on their own. In contrast, chronic hepatitis remains silent for decades before becoming symptomatic, hence physicians need to suspect and actively search for it.



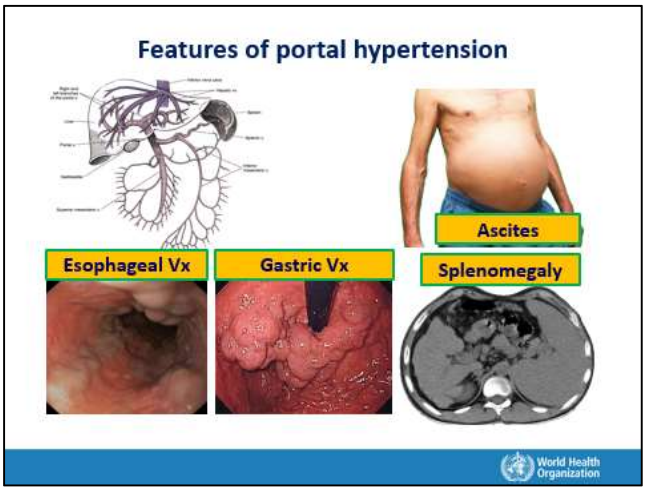
The majority of patients with chronic hepatitis are asymptomatic and are accidentally identified when screened for some other reason such as presurgical work-up, pre-visa screening, antenatal screening, etc. In the later stages of fibrosis, the patient may present with various combinations of jaundice, deranged liver function tests or features of portal hypertension.



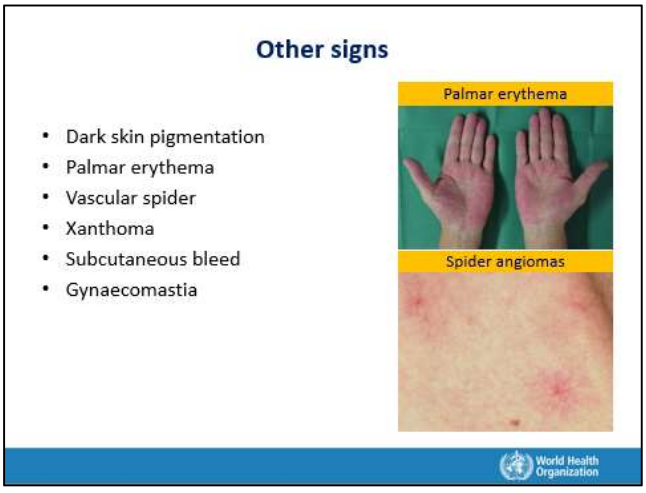
Chronic liver disease (CLD) has no specific feature. The features of CLD are common non-specific features. The features of decompensation such as ascites, bleeding, encephalopathy appear at a very late stage of the disease.



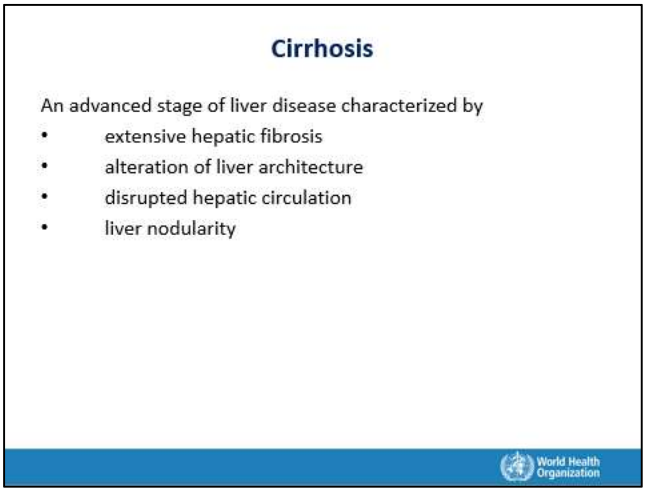
There are three major functions of the liver: glucose metabolism, which maintains the blood glucose within an acceptable range; excretion of waste substances from body in the bile; and synthesis of important body proteins such as albumin and coagulation factors. Impaired glucose metabolism results in postprandial hyperglycaemia and hypoglycaemia after fasting. Impaired excretion of bilirubin results in jaundice. Impaired clearance of toxic wastes may lead to unconsciousness. Albumin is the main protein that maintains the oncotic pressure of the blood and keeps the body vascular volume maintained. If albumin not synthesized then fluid will move out from the blood vessels to spaces such as the peritoneal cavity and pleural cavities. It results in ascites and pleural effusion. Impaired synthesis of coagulation factors will lead to bleeding manifestations.

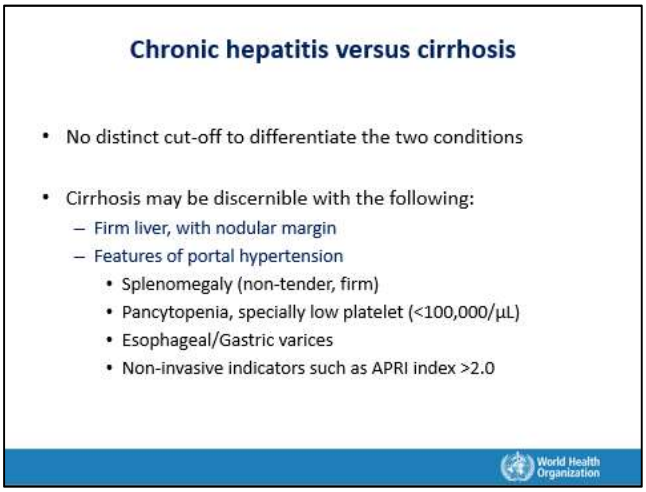


Vasculature proximal to liver gets congested, which is known as portal hypertension. Portal hypertension results in appearance of varices, splenomegaly, ascites, etc. Portal hypertension results in collateral formation at various places. The newly formed collateral vessels manifest as esophageal varices or gastric varices.

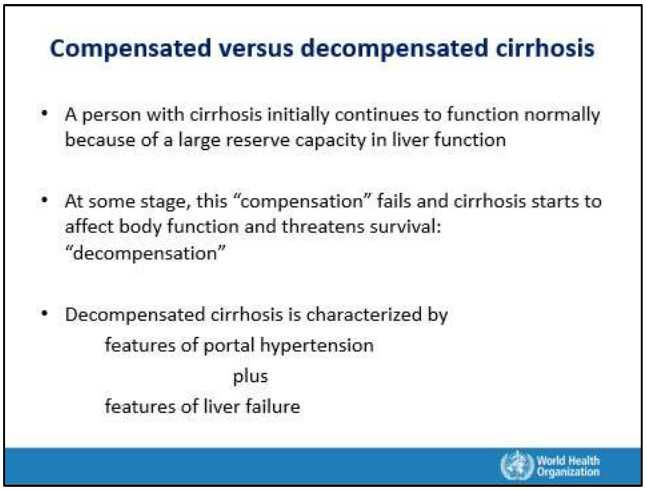


These are a few features which are found in patients with liver cirrhosis. These features helps in early suspicion of cirrhosis by a simple clinical examination.

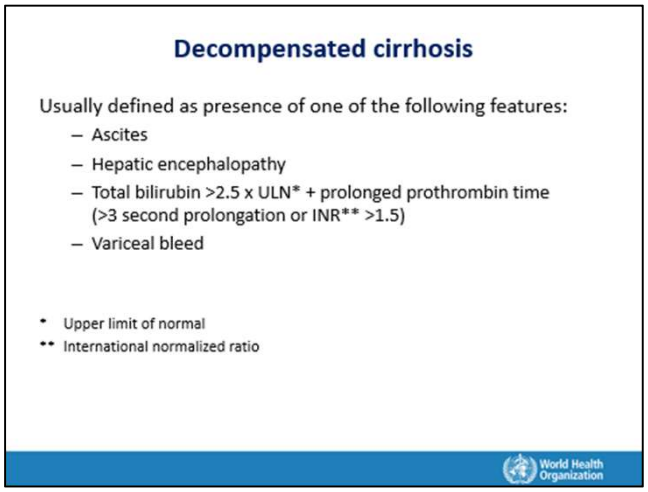




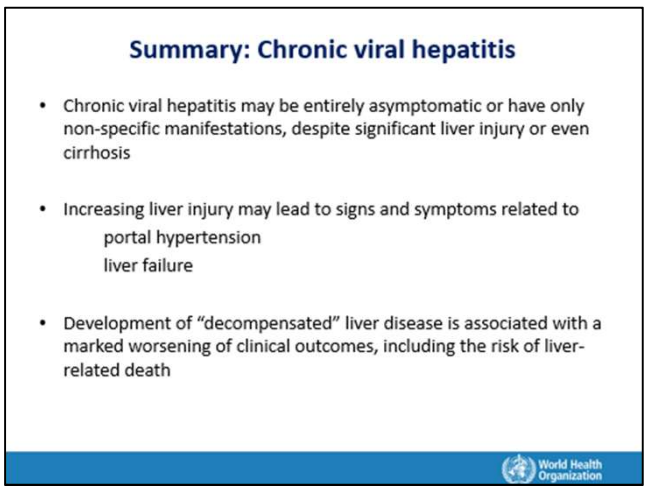
As we know, liver fibrosis in chronic hepatitis is a continuous process and the severity of fibrosis extends from F1 to F4. Fibrosis stage F4 is also called cirrhosis. Clinically, cirrhosis is characterized by the presence of a small, hard liver, which has a nodular surface and irregular margins. In addition, patients with cirrhosis also have features of portal hypertension.

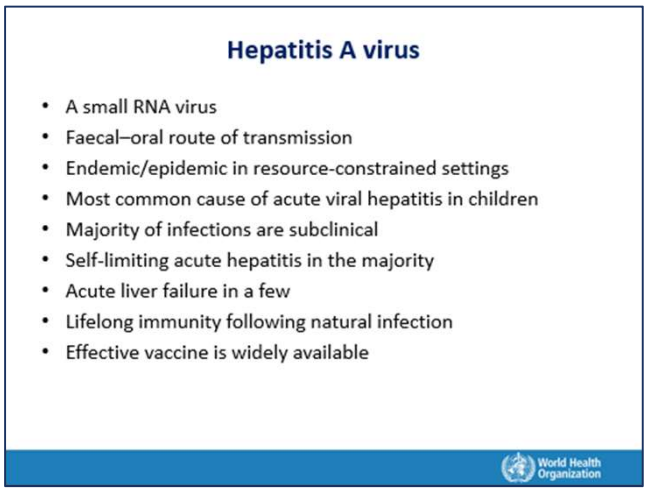


Cirrhosis has two stages: compensated and decompensated. A person with cirrhosis initially continues to function normally because of a large reserve capacity in liver function At some stage, this "compensation" fails, and cirrhosis starts to affect body functions and threatens survival: "decompensation" Decompensated cirrhosis is characterized by features of portal hypertension plus features of liver failure.



Decompensation is defined by the presence of any of the four features as described above. Even if the ascites resolves, a patient will still be oconsidered as decompensated.





Hepatitis B virus

- Circular DNA genome
- Parenteral transmission:
  - Contaminated blood
  - Unsafe injections
  - Unprotected sex, mother-to-child
- Risk of developing chronic infection depends upon the age of the person
- Self-resolving acute hepatitis in adults
- Chronic infection continues throughout life in the majority
- Chronic infection >chronic hepatitis >cirrhosis >liver cancer
- Highly effective vaccine is available

World Health Organization

Hepatitis C virus

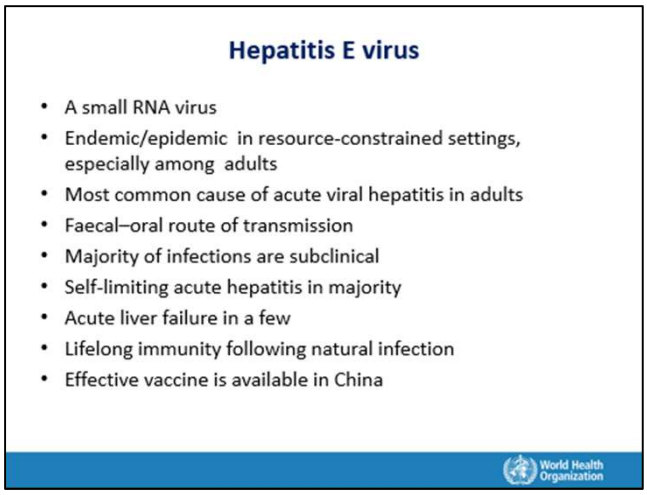
- Genome is made up of RNA
- Parenteral transmission: use of contaminated blood/sharp instruments, unprotected sex, pregnant mother to child
- Low risk for sexual and mother-to-child transmission
- Acute infection goes unnoticed
- Majority (70%) of infected persons develop chronic infection
- Chronic infection >chronic hepatitis >cirrhosis >liver cancer
- Chronic infection can easily be treated now
- No vaccine is available

World Health Organization

Hepatitis D virus

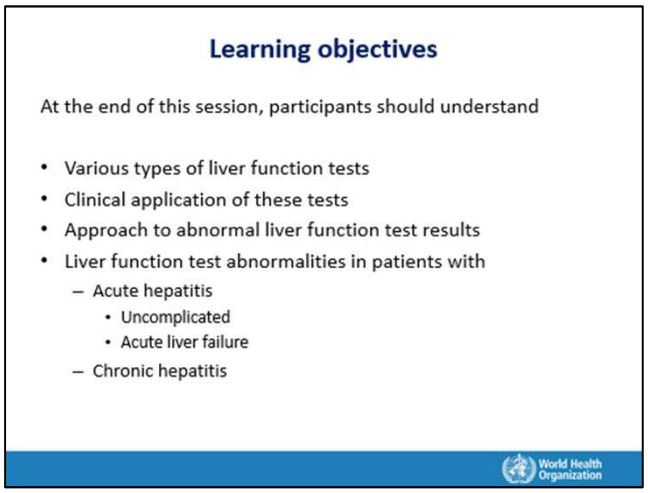
- An incomplete RNA virus
- Can cause infection in the presence of hepatitis B virus infection
- People with chronic HBV infection are at risk for acquiring HDV infection
- Parenteral transmission
- Oral drugs effective against HBV are ineffective against HDV
- Treated with pegylated interferon
- Hepatitis B vaccination prevents against HBV infection

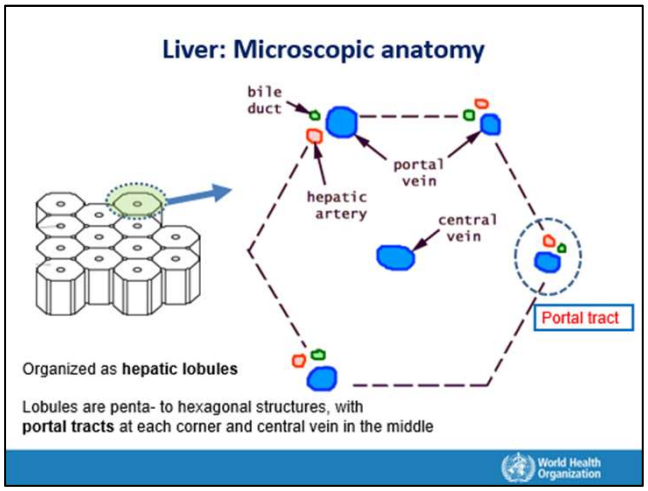
World Health Organization


Hepatitis E virus
A small RNA virus
Endemic/epidemic in resource-constrained settings, especially among adults
Most common cause of acute viral hepatitis in adults
Faecal–oral route of transmission
Majority of infections are subclinical
Self-limiting acute hepatitis in majority
Acute liver failure in a few
Lifelong immunity following natural infection
Effective vaccine is available in China
World Health Organization

Module 4

Interpretation of liver function tests





Each liver lobule has the following 3 structures in each corner of its hexagon: bile duct (green), portal vein (blue) and hepatic artery (pink). Usually there is one of each of these but sometimes there may be 2–4 bile ducts and sometimes only 2 structures. In the centre of each lobule there is one central vein (blue), which drains into the hepatic veins.

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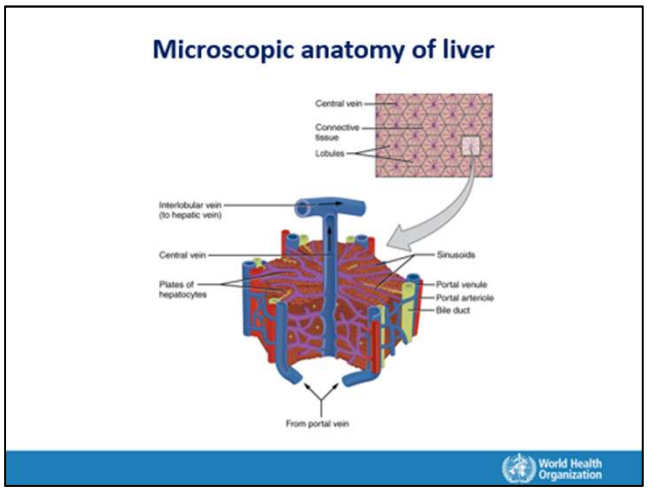
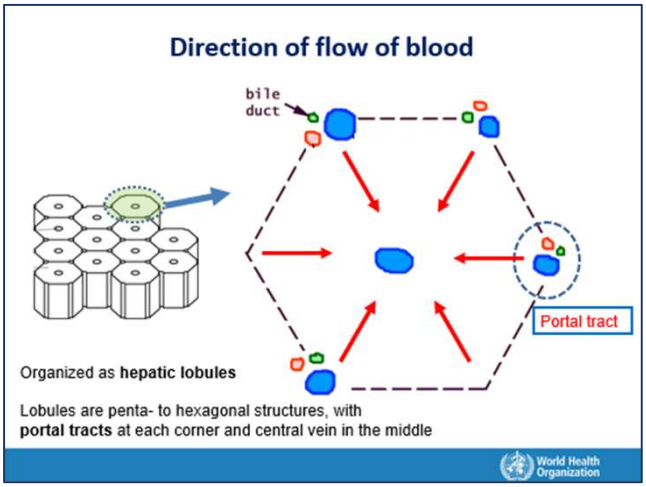
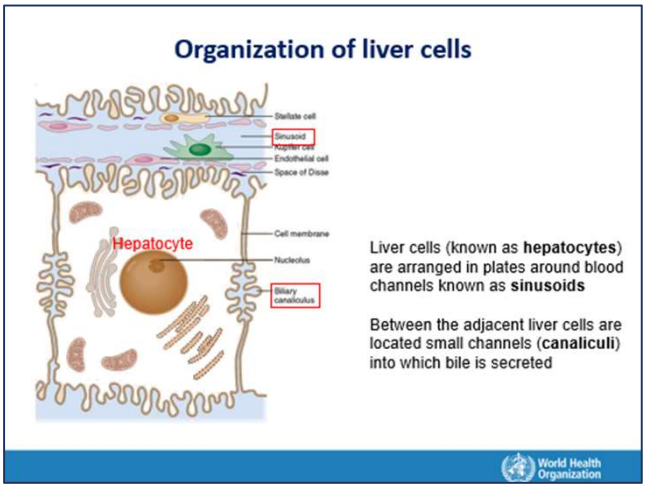


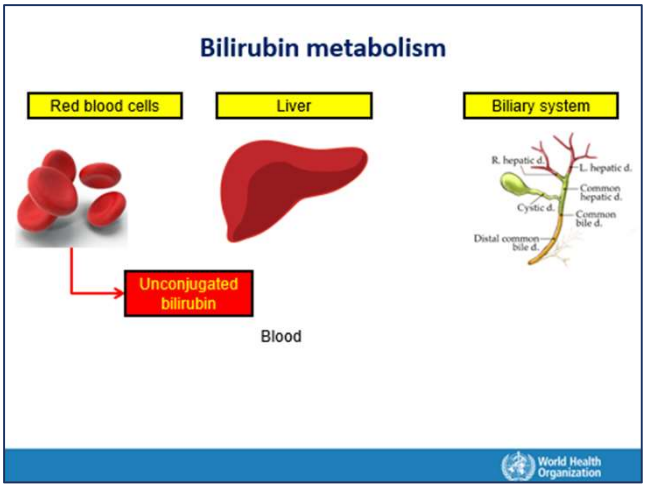
This is a three-dimensional picture of a hexagonal liver lobule. Each lobule is a three-dimensional structure, which shows the portal tract at each of the corner. Each portal tract has a branch of the portal vein (blue), hepatic artery (red) and bile duct (light green). The entire lobule is packed with hepatocytes organized in the form of plates (brown), which are separated by blood-filled sinusoids (purple).

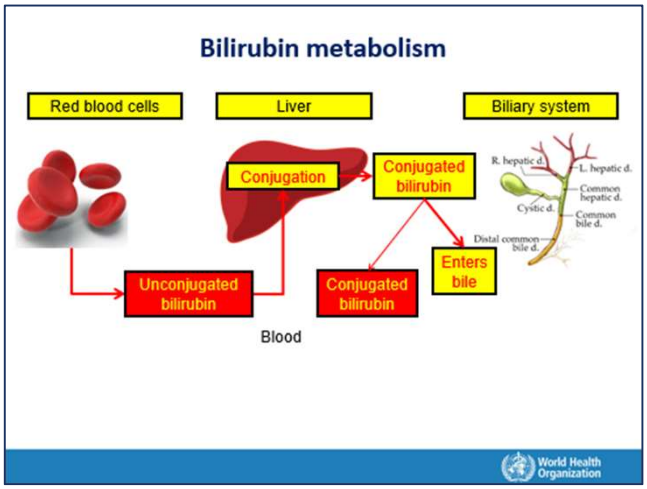


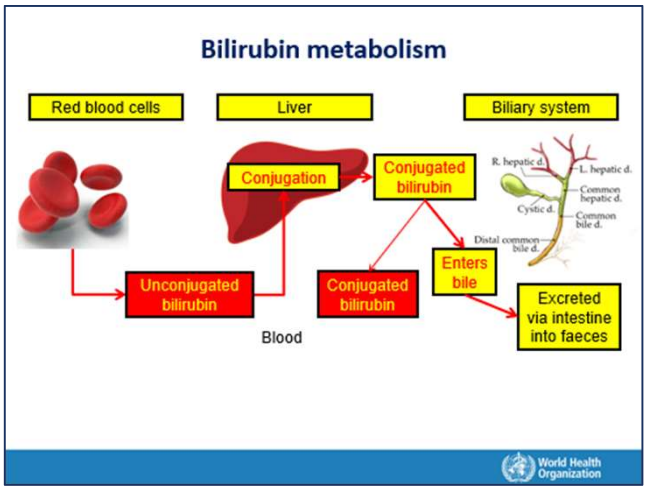
In each lobule, blood from the branches of the portal vein and hepatic artery enters from the corner and flows in a centripetal direction to drain into the central vein. This flow of blood is slow and under low pressure, which gives adequate time for exchange between the blood and surrounding hepatocytes.

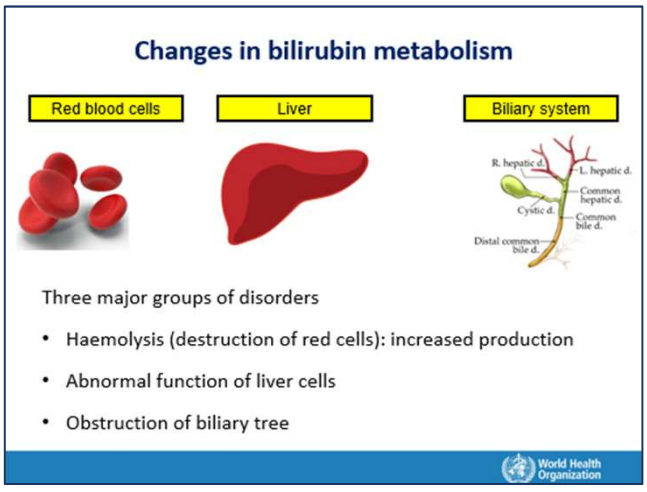


Liver cells are hexagonal in shape and are arranged in the form of “plates of cells”. The surfaces of these hepatocyte plates are lined with sinusoidal cells and the spaces between the two adjacent hepatocyte plates are called “sinusoids”. Venous blood, carried into the liver through the portal vein, flows into these sinusoids. Hence, each hepatocyte is bathed in nutrient-rich portal venous blood along its surface. Inside the hepatocyte plates, the adjoining surfaces of each hepatocyte abut the “bile canaliculi”. These canaliculi collect bile secreted by each hepatocyte and drain into the biliary tree.



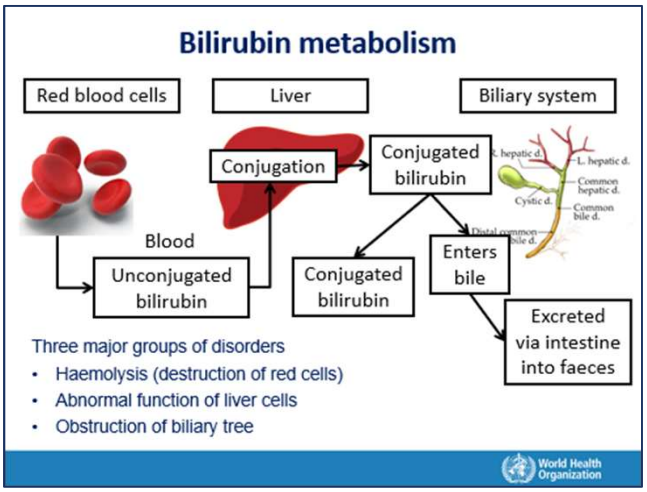




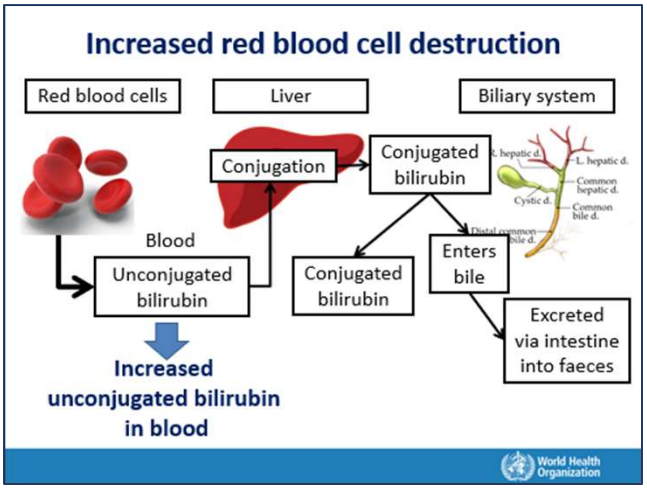


Bilirubin is a substance that is made when your body breaks down old red blood cells. This is a normal process. Bilirubin is also part of the bile that your liver makes to help digest the food you eat. A small amount of bilirubin is normally present in your blood. Healthy adults make 250 to 350 mg of bilirubin each day. Bilirubin that is bound to a certain protein (albumin) in the blood is called unconjugated, or indirect, bilirubin. Conjugated, or direct, bilirubin travels from the liver into the small intestine. A very small amount passes into your kidneys and is excreted in the urine. This bilirubin also gives urine its distinctive yellow colour.

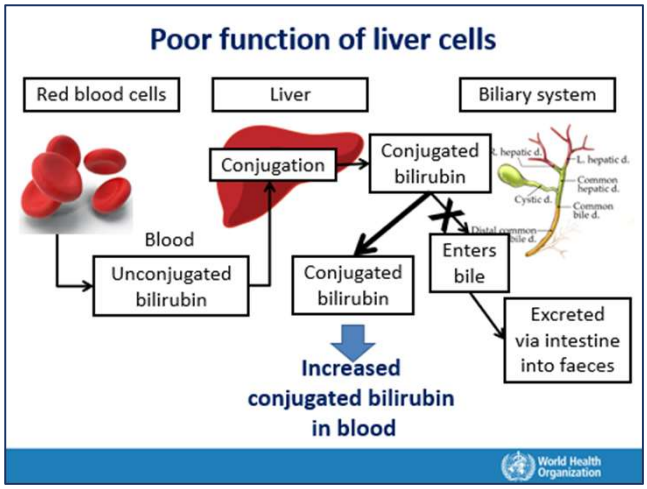
Module 4



Jaundice is one of the most common clinical feature in patients with liver disease such as viral hepatitis. Clinical jaundice represents the elevated serum level of bilirubin. Bilirubin metabolism includes three steps: first, production of unconjugated bilirubin by the destruction of old red blood cells; second, conversion of unconjugated bilirubin into conjugated bilirubin in the liver; and third, excretion of conjugated bilirubin into bile as pile pigment through the biliary tract. Diseases affecting any of these three steps may lead to jaundice. The pattern of elevation of bilirubin and liver enzymes helps us to differentiate between the causes of jaundice.

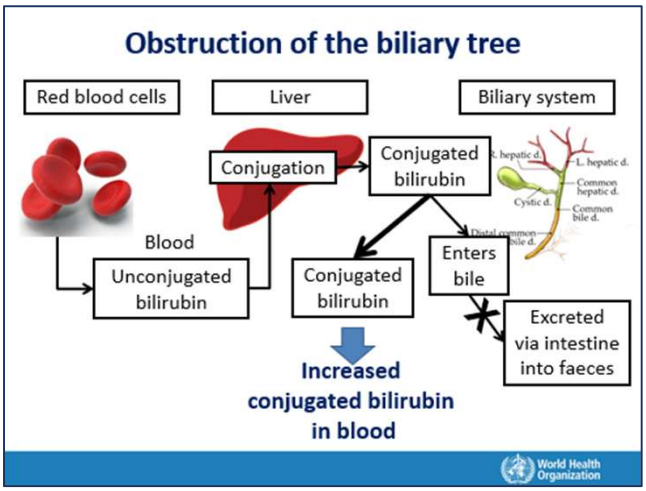


Excessive destruction (called haemolysis) of red blood cells, regardless of its cause, will result in haemolytic or unconjugated jaundice. Haemolytic jaundice is commonly seen in patients with haemoglobinopathies such as sickle cell anaemia, thalassaemia, etc. Most of the haemolysis in our body takes place in the spleen and hence majority of the patients with haemolytic jaundice also have splenic enlargement. In most patients, an enlarged spleen is firm and non-tender. In addition, the majority of patients with haemolysis will also have anaemia or low haemoglobin.

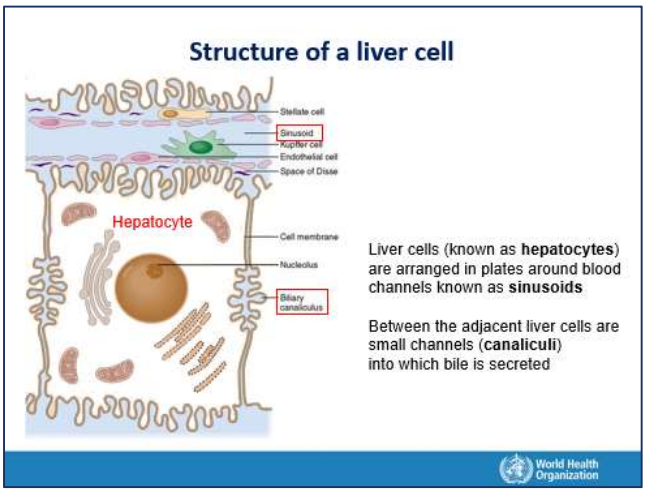


The liver in involved in two steps of bilirubin metabolism: conjugation of unconjugated bilirubin and excretion of conjugated bilirubin. Injuries or diseases affecting the hepatocytes result in a reduction of both of these liver functions but the excretory function is more affected than the conjugatory function. In the presence of liver diseases such as viral hepatitis or liver cirrhosis, conjugated bilirubin is not completely excreted in the bile but is released into the circulation, which results in a mixed pattern of jaundice with a predominance of conjugated bilirubin.

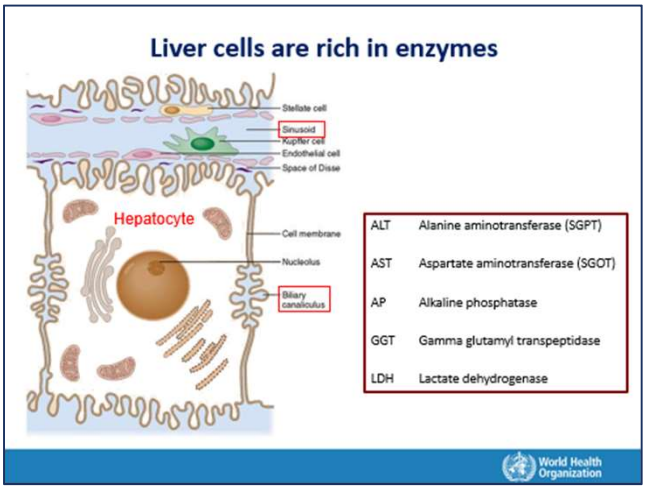
Module 4



Several diseases could cause obstruction of the biliary tract. These diseases neither affect the conjugation of bilirubin in the liver nor affect the excretion of conjugated bilirubin from the liver into the bile but they stop the flow of bile into the biliary tree. Because of excessive accumulation, bile is refluxed from the liver into the circulation and results in conjugated hyperbilirubinaemia. The most common causes of biliary tract obstruction are gallstone disease, carcinoma of the gallbladder, cholangiocarcinoma, etc.



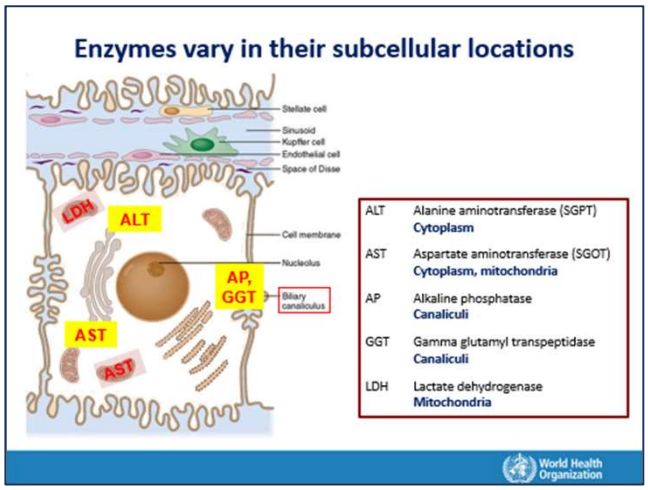
Liver function tests include estimation of the serum levels of four important enzymes in the liver. An increase in the serum levels of these enzymes indicates liver injury. Each of these enzymes is located in specific areas within the hepatocytes and cholangiocytes. Liver injury, induced by various inciting agents such as toxins, pathogens, etc. follows one of the three injury patterns: hepatocellular, cholestatic and mixed patterns. These patterns of liver injuries manifests in form of a particular pattern of elevation of specific liver enzymes. Hepatitis viruses primarily produce a hepatocellular pattern of liver injury, which is characterized by very high serum levels of the enzymes ALT and AST; serum levels of alkaline phosphatase and gamma glutamyl transpeptidase (GGT) are either normal or mildly elevated.

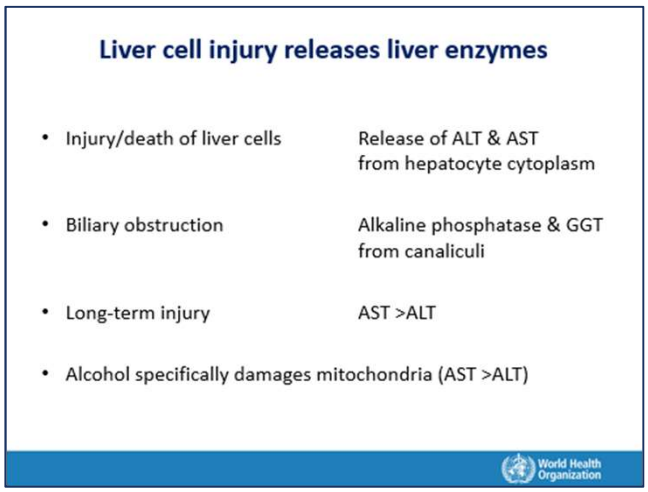


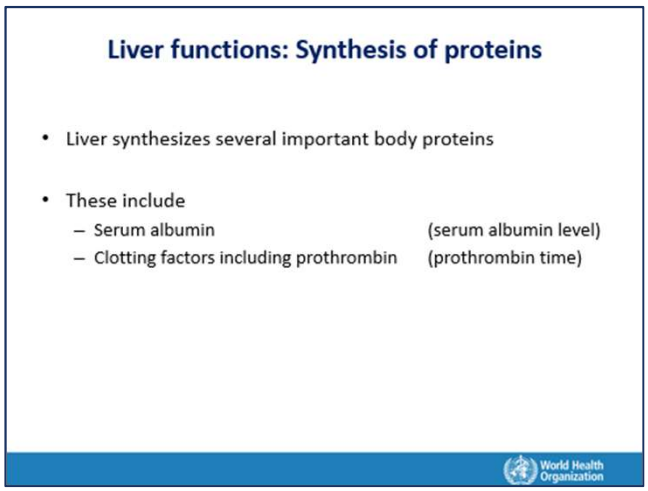
Infection with the hepatitis viruses results in sudden and massive necrosis of the hepatocytes, which leads to the release of ALT and AST enzymes from the cell cytoplasm into the blood circulation.

Patients with viral hepatitis frequently have jaundice. We must remember that jaundice in a given patient could also be because of biliary obstruction; hence, we need to differentiate between these two different causes of jaundice, whether due to hepatitis viruses or biliary obstruction.

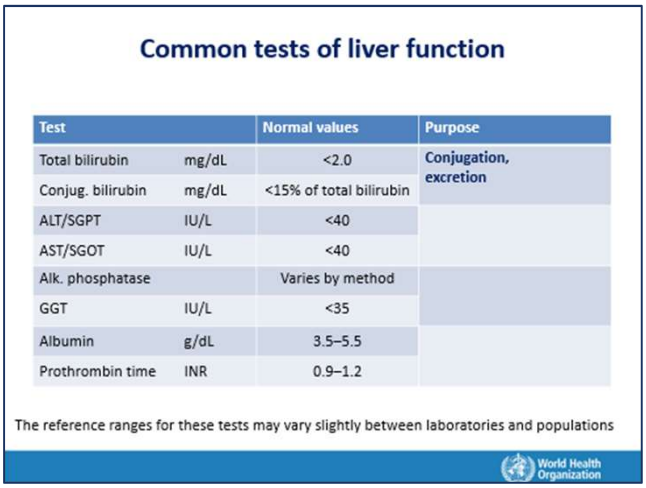
In a jaundiced patient, infection with the hepatitis viruses results in very high serum levels of ALT and AST in contrast to a patient with biliary obstruction, in whom serum levels of alkaline phosphatase and GGT are markedly elevated but ALT/AST are mildly elevated.







The liver plays several important roles in our body. The two most important functions of the liver are its synthetic function and excretory function. The synthetic capabilities of the liver are estimated by serum levels of the proteins synthesized and released by the liver. The two most important such proteins are albumin and clotting factors. In a person with liver disease, if the synthetic function of liver is compromised, it will result in two important problems. First, low serum albumin causes bilateral pitting-type pedal edema, ascites or anasarca. Second, impaired synthesis of clotting factors results in prolongation of the prothrombin time, which may cause spontaneous bleeding such as ecchymosis. The liver normally excretes bilirubin, which is a waste product of haemoglobin metabolism. Bilirubin is normally excreted in the bile and expelled in the faeces. In the presence of impaired excretory function, bilirubin starts accumulating in the blood and manifests as jaundice or yellow discolouration of the eyes and urine.



Common tests of liver function

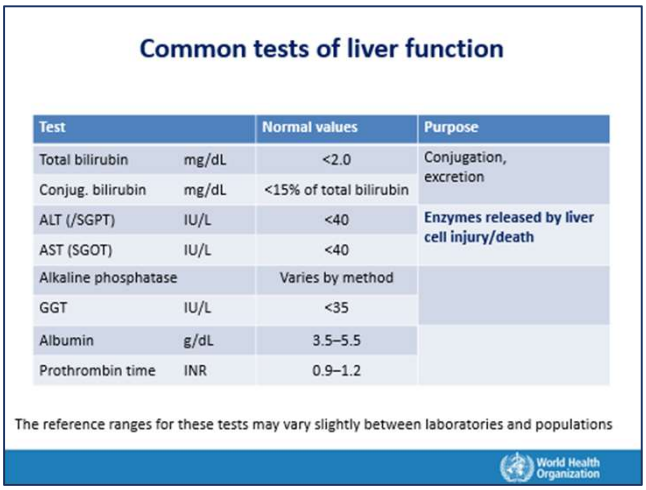
Test		Normal values	Purpose
Total bilirubin	mg/dL	<2.0	Conjugation, excretion
Conjug. bilirubin	mg/dL	<15% of total bilirubin	
ALT/SGPT	IU/L	<40	
AST/SGOT	IU/L	<40	
Alk. phosphatase		Varies by method	
GGT	IU/L	<35	
Albumin	g/dL	3.5–5.5	
Prothrombin time	INR	0.9–1.2	

The reference ranges for these tests may vary slightly between laboratories and populations

World Health Organization

Liver function tests is a name given to a set of biochemical tests. Each of these tests evaluates a specific function of liver cells.

Total bilirubin and conjugated bilirubin tell about the conjugatory and excretory functions of hepatocytes.



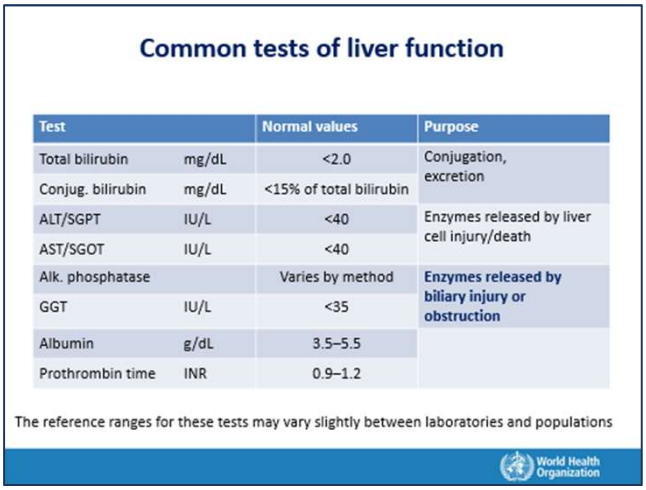
Common tests of liver function

Test		Normal values	Purpose
Total bilirubin	mg/dL	<2.0	Conjugation, excretion
Conjug. bilirubin	mg/dL	<15% of total bilirubin	
ALT (/SGPT)	IU/L	<40	Enzymes released by liver cell injury/death
AST (SGOT)	IU/L	<40	
Alkaline phosphatase		Varies by method	
GGT	IU/L	<35	
Albumin	g/dL	3.5–5.5	
Prothrombin time	INR	0.9–1.2	

The reference ranges for these tests may vary slightly between laboratories and populations

World Health Organization

Serum ALT (which was earlier known as SGPT) and serum AST (which was earlier known as SGOT) are released from the hepatocytes into the circulation after hepatocyte injury or death.



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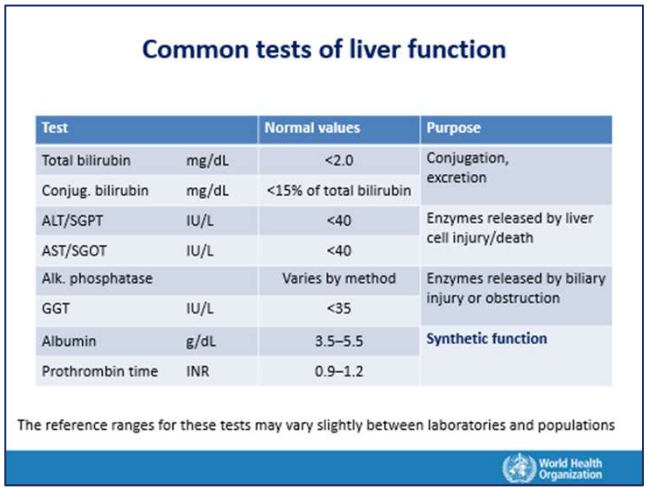
ALT/SGPT	IU/L	<40	Enzymes released by liver cell injury/death
AST/SGOT	IU/L	<40	
Alk. phosphatase		Varies by method	Enzymes released by biliary injury or obstruction
GGT	IU/L	<35	
Albumin	g/dL	3.5–5.5	
Prothrombin time	INR	0.9–1.2	

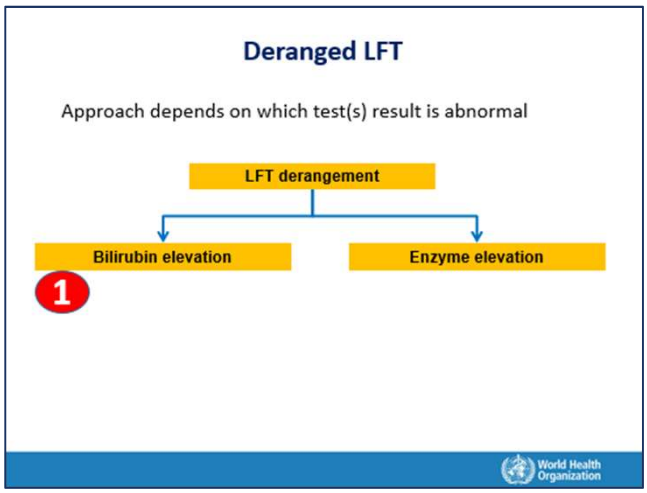
The reference ranges for these tests may vary slightly between laboratories and populations

World Health Organization

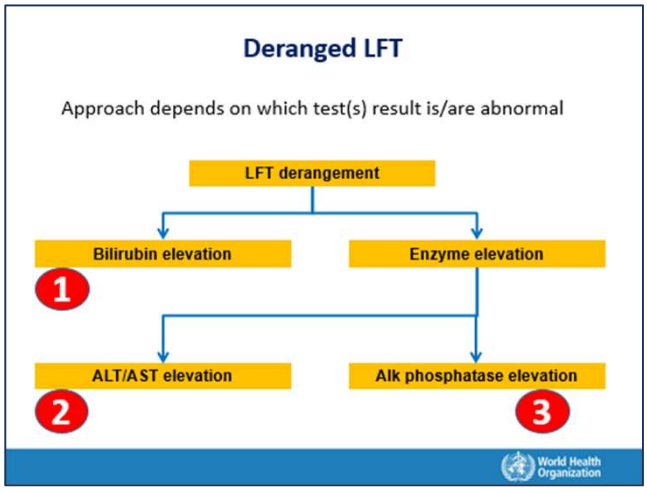
Serum alkaline phosphatase and GGT are located in the cholangiocytes and represent their injury or death. Cholangiocytes are injured in biliary tract diseases such as cholangitis, biliary obstruction, etc.



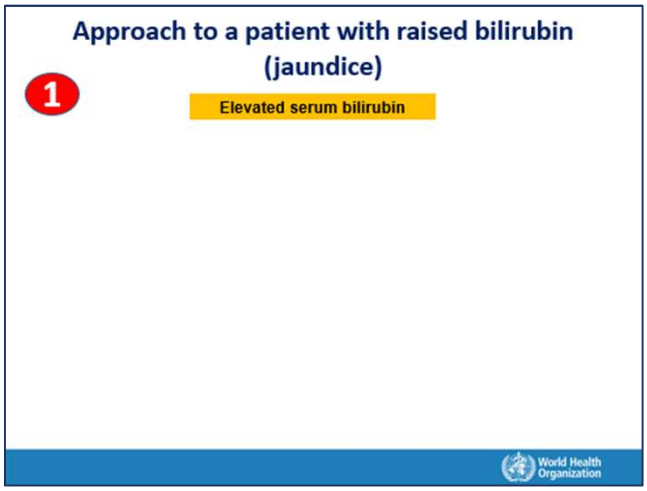
Serum albumin and prothrombin time are markers of the synthetic functions of the liver.



Liver function tests has two components: bilirubin and various liver enzymes. For a complete and accurate interpretation of LFT in a person, we need to look at them carefully. If liver enzymes are predominantly elevated than bilirubin then we need to look which group of enzymes are elevated: those located inside the hepatocytes such as ALT and AST, or those located inside the cholangiocytes such as alkaline phosphatase and GGT.



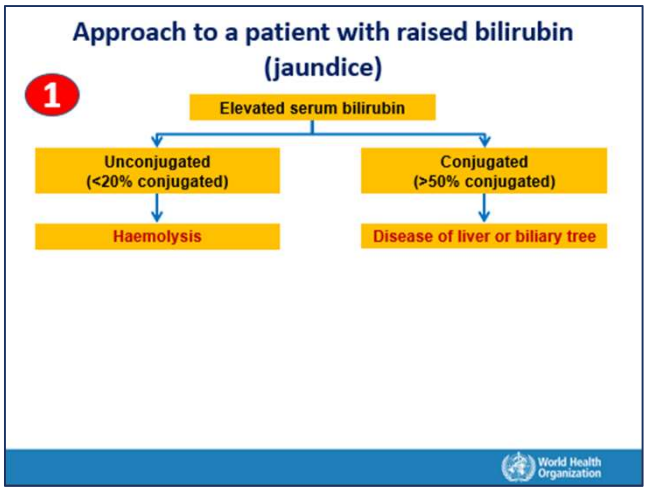
Liver function tests have two components: bilirubin and various liver enzymes. For complete and accurate interpretation of LFT in a person, we need to look at these carefully. If liver enzymes are predominantly elevated rather than bilirubin, then we need to look which group of enzymes are elevated: those located within the hepatocytes such as ALT and AST ; or those located inside the cholangiocytes such as alkaline phosphatase and GGT.



In a person with jaundice, the first thing we need to see is the proportions of conjugated and unconjugated bilirubin. The presence of less than 20% unconjugated bilirubin fraction indicates an underlying haemolytic disorder. On the other hand, if the fraction of conjugated bilirubin is more than 50%, it is known as conjugated hyperbilirubinaemia and indicates the presence of liver or hepatobiliary disease.

Once conjugated hyperbilirubinaemia has been identified, we need to do an ultrasound abdomen (USG). The radiologist will be informed about what we need to see in the USG. The USG would look for evidence of the following: (i) biliary obstruction such as dilatation of the biliary tract, gallbladder mass or any other mass in the liver; (ii) evidence of chronic liver disease such as liver size, smooth or nodular liver surface, regular or irregular liver margin, portal vein dilatation (normal <12 mm), spleen size, presence of venous collaterals at the splenic hilum and around the portal vein, presence of ascites, etc. A good ultrasound examination can reliably differentiate between liver disease and biliary tract disease as a cause for conjugated hyperbilirubinaemia.

The next step, after the possibility of biliary obstruction has been excluded, is to look into the pattern of liver enzyme elevation, which helps us to identify the possible cause of the liver disease. There are three patterns of liver injury: hepatocellular, cholestatic and mixed patterns. In the hepatocellular pattern of liver injury, there is marked elevation of ALT and AST. In cholestatic liver injury there is marked elevation of alkaline phosphatase and GGT. Patients with a mixed pattern have a variable combination of liver enzyme elevation.



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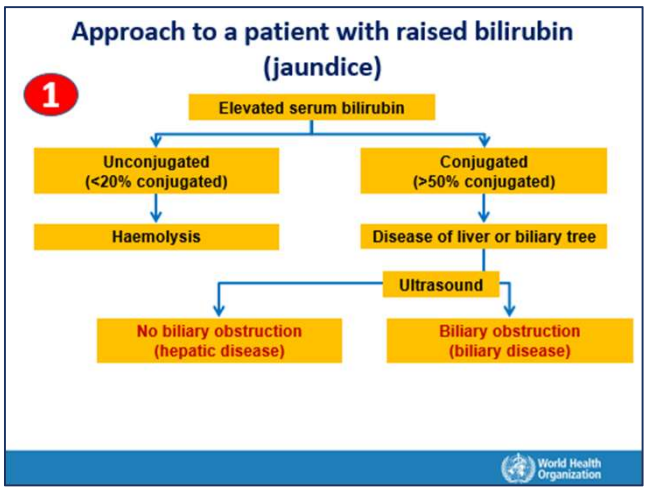

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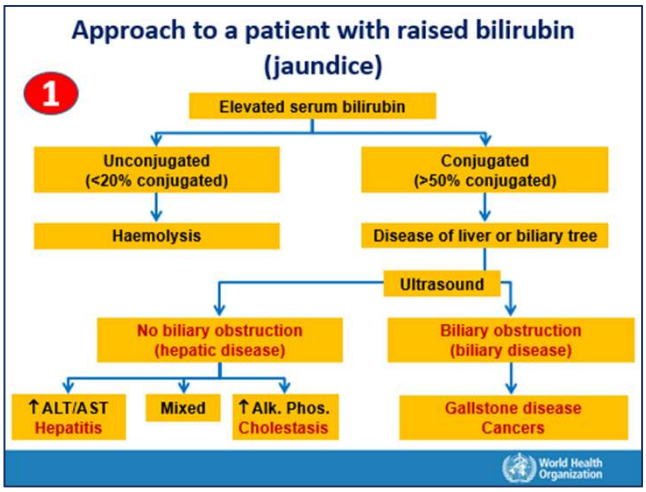
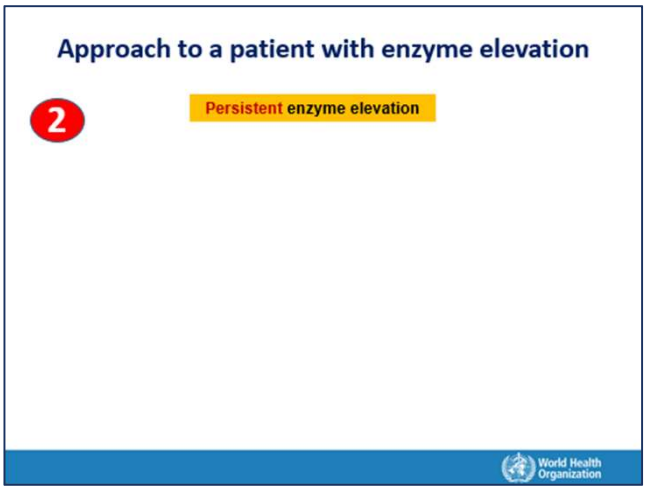
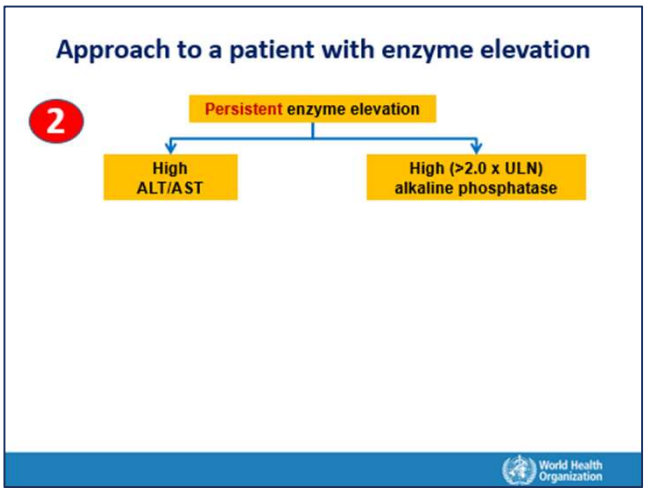
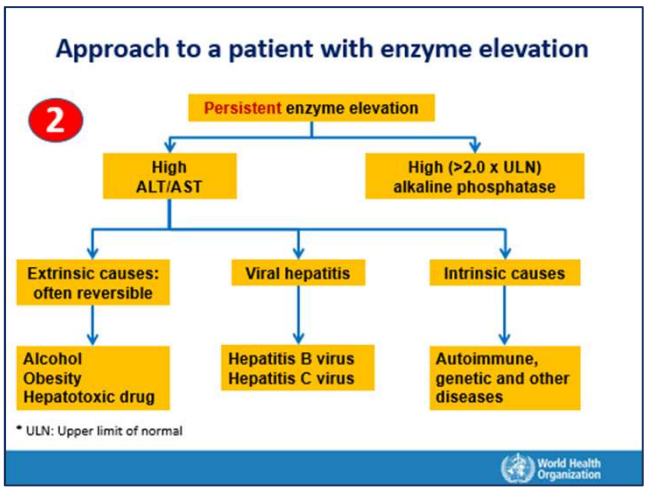


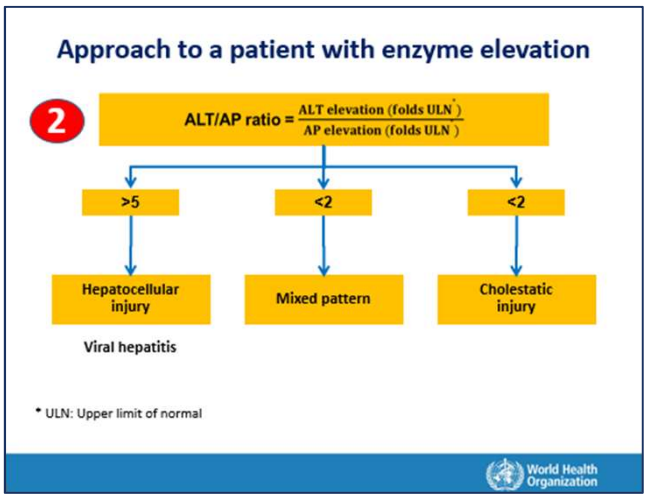


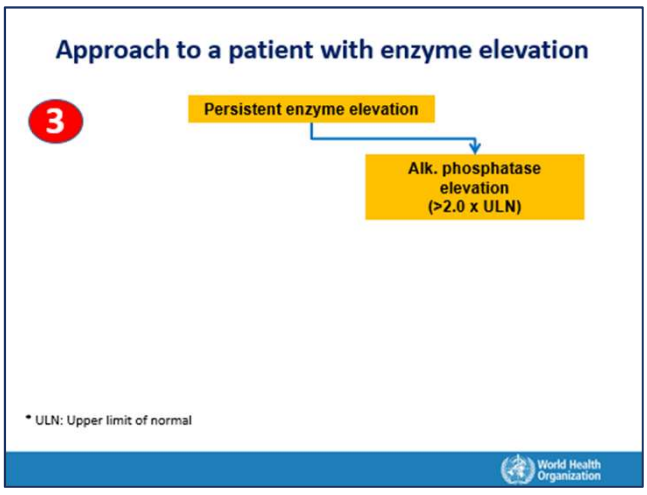


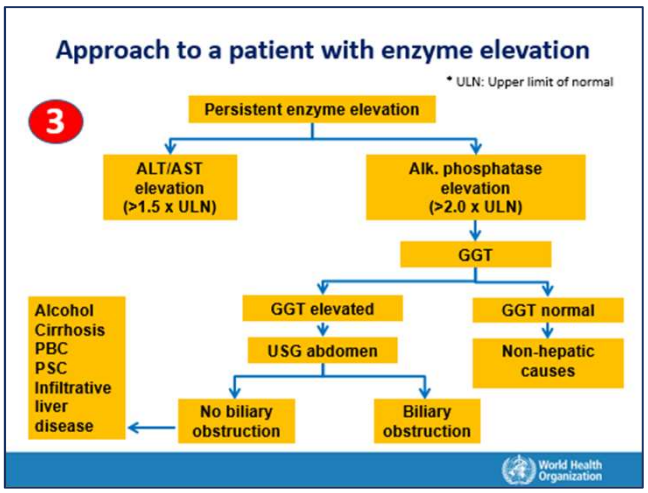
Hepatocellular injury may have several causes. The most important causes for marked elevation of ALT/AST are viral hepatitis, alcoholic liver disease, drug-induced liver injury, and autoimmune hepatitis.

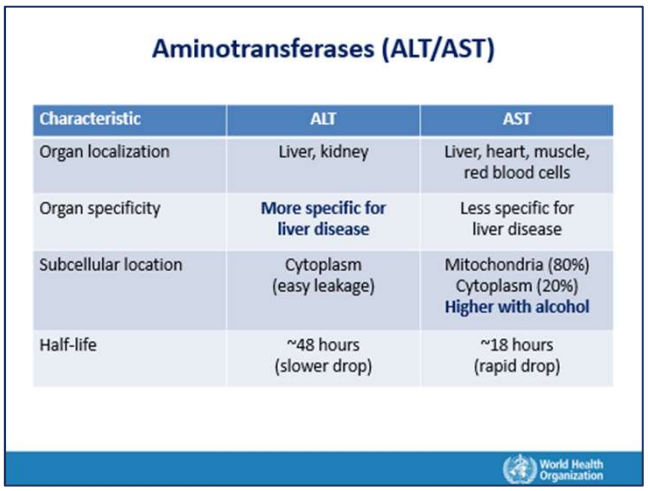
Cholestatic liver injury is primarily caused by drugs, liver infiltration due to bacterial (such as tuberculosis) or fungal infections, storage diseases such as amyloidosis, or biliary tract disorders such as primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), etc.


Approach to a patient with enzyme elevation
2
Persistent enzyme elevation
High ALT/AST
High (>2.0 x ULN) alkaline phosphatase
Extrinsic causes: often reversible
Viral hepatitis
Intrinsic causes
Alcohol
Obesity
Hepatotoxic drug
Hepatitis B virus
Hepatitis C virus
Autoimmune, genetic and other diseases
* ULN: Upper limit of normal
World Health Organization


Approach to a patient with enzyme elevation
2
ALT/AP ratio = ALT elevation (folds ULN*) / AP elevation (folds ULN*)
>5
<2
<2
Hepatocellular injury
Mixed pattern
Cholestatic injury
Viral hepatitis
* ULN: Upper limit of normal
World Health Organization


Approach to a patient with enzyme elevation
3
Persistent enzyme elevation
Alk. phosphatase elevation (>2.0 x ULN)
* ULN: Upper limit of normal
World Health Organization



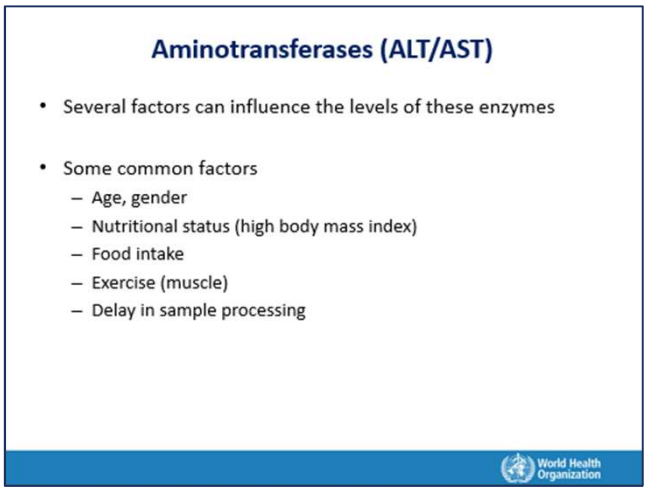


ALT and AST are two separate enzymes, which are used as markers of liver injury. It is common to see them as synonymous with each other. These two enzymes differ markedly from each other and have their own clinical significance.

ALT is primarily is located in the liver and hence it is a more specific enzyme for liver injury than AST, which is more widely distributed in the body. Serum AST levels are frequently elevated in the presence of heart disease such as ischaemic heart disease, haemolysis and muscle injury.
Further, ALT is located in the cytoplasm of the hepatocytes and hence is released by minor injury. This makes ALT a sensitive marker of liver injury.

AST is primarily located inside the mitochondria, and is also found in the cytoplasm of the hepatocyte in a relatively low concentration. AST is released from the hepatocyte after more severe injury, in particular, after injury with an agent that causes injury to the mitochondria such as alcohol.
Hence, AST is a less sensitive and less specific marker of liver injury than ALT. AST is more elevated than ALT in alcohol-induced liver injury.
One important aspect is that ALT has a longer half-life than AST. Hence, the serum ALT level takes a longer time to normalize than the AST after the injury has subsided.

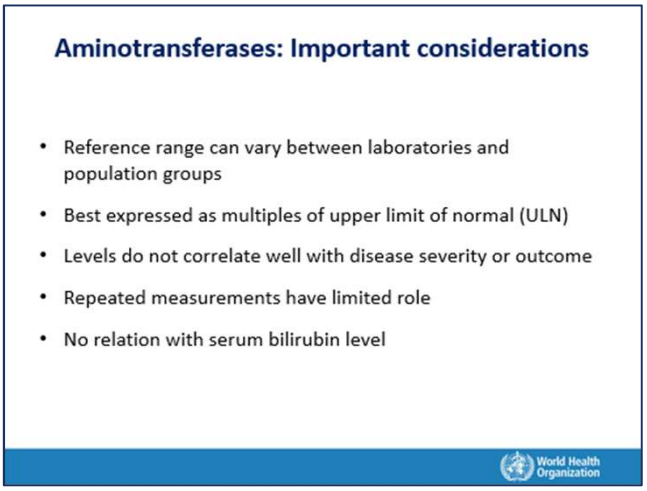
ALT is indicator of liver injury and AST is indicative of fibrosis. So ALT is used in hep B management while AST is used in Hep C management



In patients with viral hepatitis, in particular, those with hepatitis B infection, serum ALT and AST levels are the cornerstone of diagnosis and management. We need precise estimation of their serum levels. Even a slight change in serum ALT/AST level could change the diagnosis, management and follow-up plan for a given patient.

The serum levels of ALT and AST are sensitive to several common factors such as age, gender, body build (because of liver size, metabolic requirement of the body and muscle mass), fed or fasting state (because liver enzymes are needed for normal metabolism in the liver), exercise (because AST may be released from the muscle after exercise), and delay in sample processing (because AST may be released from the RBCs present in collected blood).

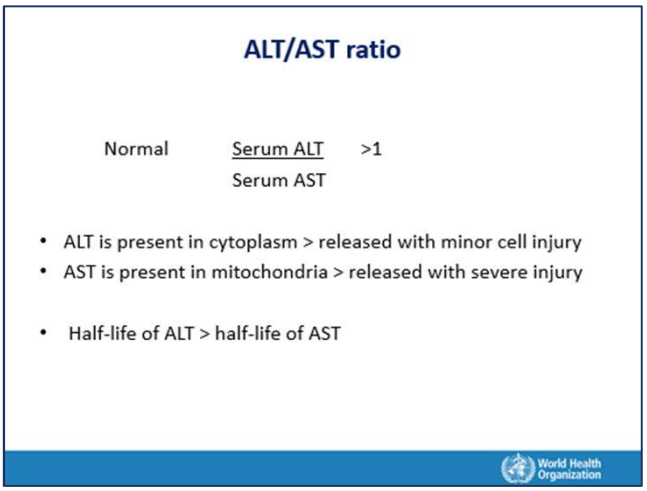
Hence, we must ensure that blood specimens for ALT/AST estimation are collected in the morning after overnight fasting because this will obviate the effect of diet and exercise on serum enzyme levels. Food can increase ALT/AST level by 2–3-fold, so it should be tested while fasting in the morning as morning collection also takes care of a rise due to muscle activity.



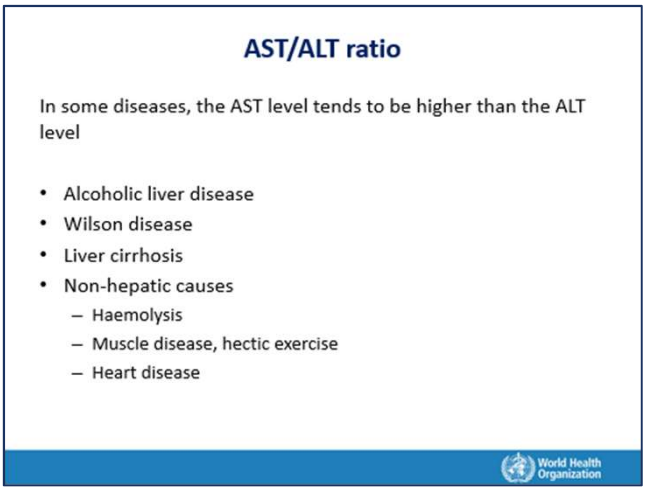
There are a few common myths about serum ALT/AST levels, which must be clarified.

Reports of serum ALT/AST levels are not uniform across the population. Usually, an ALT/AST level up to 40 IU/L is considered normal but the normal limits or reference ranges vary between populations as well as between laboratories. Hence, every value of ALT/AST should be expressed in terms of multiples of the upper limit of normal and the upper limit taken should be that of the laboratory where it is measured.

Serum levels of ALT/AST do not correlate with either liver disease severity or serum bilirubin.

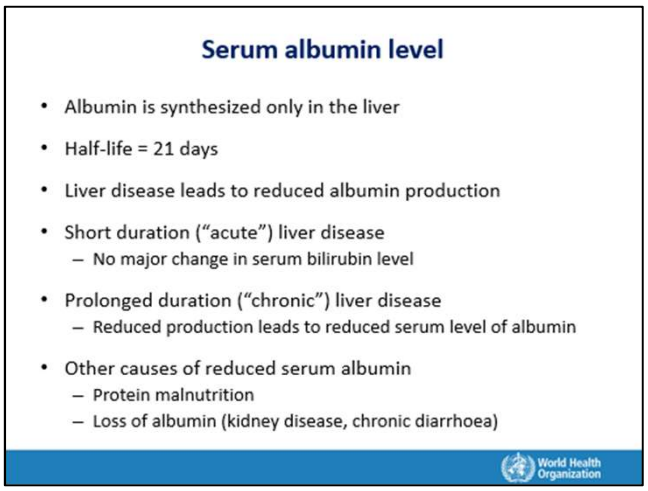


In a normal person as well as most patients with liver disease, ALT is higher than AST. There are two reasons for the higher ALT levels: first, ALT is present in the cytoplasm and is released by minor injuries; second, ALT has a longer half-life than AST and hence remains in the blood for a longer time period.



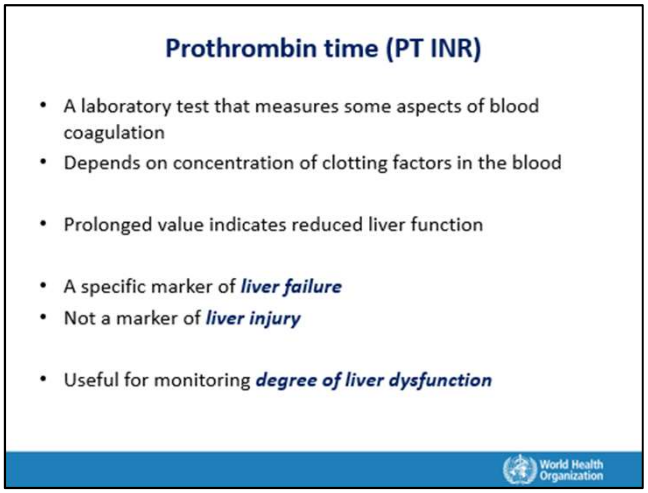
It is common practice to look at the ALT/AST ratio though it has a limited role in the diagnosis and management of liver diseases. Normal ALT levels are higher than AST levels. In certain conditions, AST could elevated more than ALT like: (i) alcoholic liver disease results in mitochondrial toxicity and pyridoxal phosphate, which is a co-factor for AST; (ii) Wilson disease results in subclinical haemolysis and release of AST; (iii) the presence of liver cirrhosis; once liver cirrhosis is established, AST remains higher than ALT because of destroyed sinusoidal architecture, which results in impaired clearance of AST.

If liver disease is excluded in a patient with a high AST, then extrahepatic sources of AST must be evaluated.



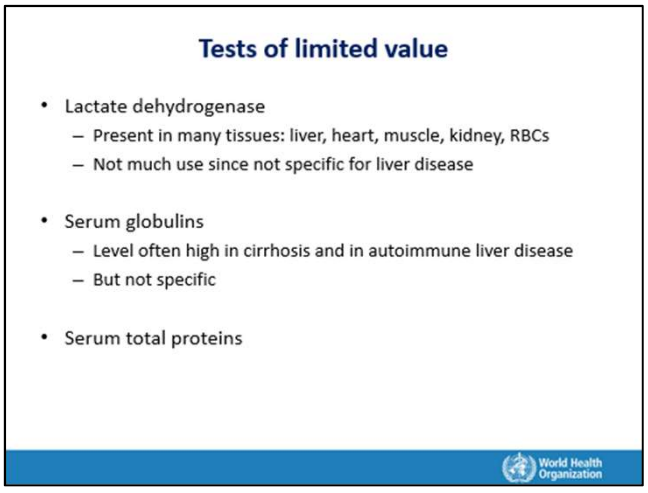
Albumin is the main body protein that maintains the oncotic pressure inside the circulatory system. It is synthesized in the liver and has a half-life of 21 days. This long half-life of albumin helps us use it as a marker to differentiate between and acute and chronic liver injuries. In acute liver injuries such as acute viral hepatitis, serum albumin levels remain normal. In contrast, in the presence of a long-standing chronic injury such as liver cirrhosis, the serum albumin is reduced.

Serum albumin may also be reduced because of excessive loss of albumin such as in patients with renal disease in whom protein is lost in the urine.

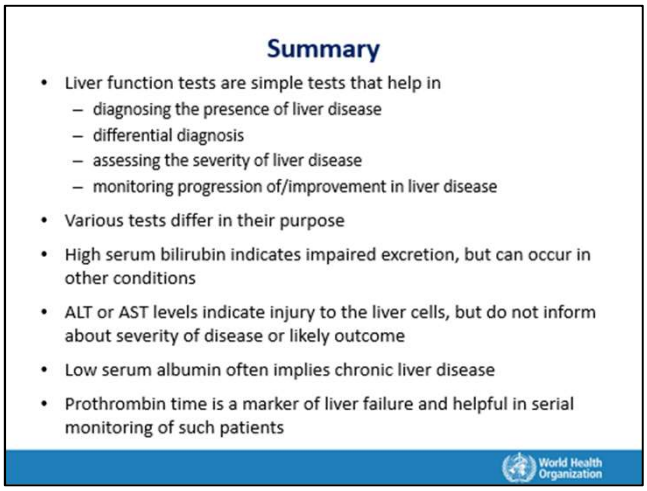


Prothrombin time, which is commonly known as PT INR, is a composite marker of serum levels of various coagulation factors synthesized in the liver. This reflects the time (in seconds) taken for blood to clot.

In the presence of significant liver disease, the synthetic functions of the liver are compromised and clotting factor levels are reduced in the serum. Reduction in clotting factors leads to prolongation of the PT INR. Mild liver injury does not cause PT prolongation. Only if a severe injury leads to liver failure is the PT prolonged. Hence PT prolongation is a marker of liver failure



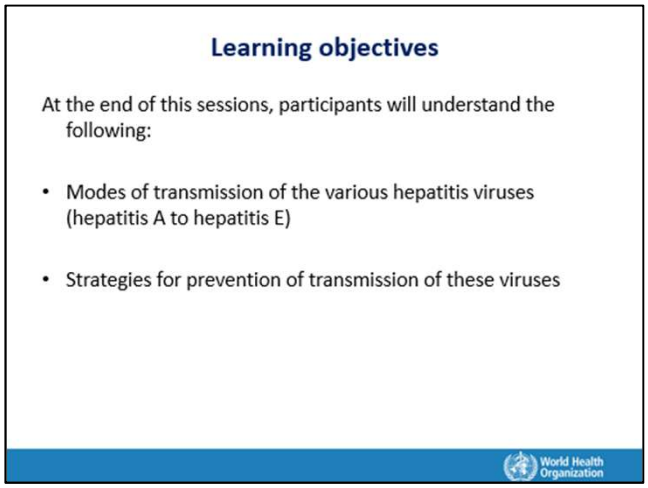
Several biochemical tests are routinely done as a part of LFT but they have very limited clinical value. These include total serum protein, lactate dehydrogenase, serum globulin, albumin/globulin ratio, etc. These tests are of little values because they are not specific for liver injury. These enzymes are located in several other organs as well and injury to those organs may cause elevation of these enzymes.


Summary
Liver function tests are simple tests that help in
diagnosing the presence of liver disease
differential diagnosis
assessing the severity of liver disease
monitoring progression of/improvement in liver disease
Various tests differ in their purpose
High serum bilirubin indicates impaired excretion, but can occur in other conditions
ALT or AST levels indicate injury to the liver cells, but do not inform about severity of disease or likely outcome
Low serum albumin often implies chronic liver disease
Prothrombin time is a marker of liver failure and helpful in serial monitoring of such patients
World Health Organization

Module 5

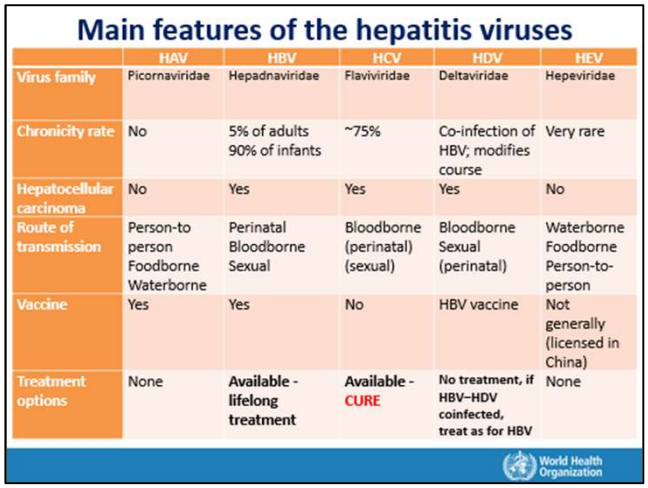
Viral hepatitis transmission and prevention

Module 5



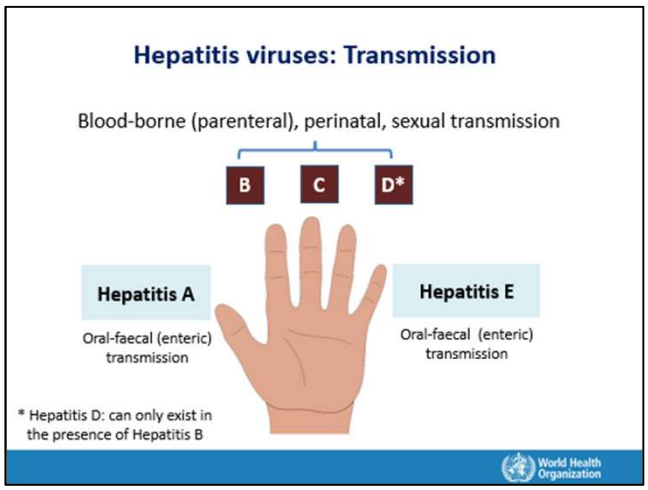
At the end of this sessions, participants should be able to understand the following:

- Modes of transmission of various hepatitis viruses (hepatitis A to hepatitis E)
- Strategies for prevention of transmission of these viruses



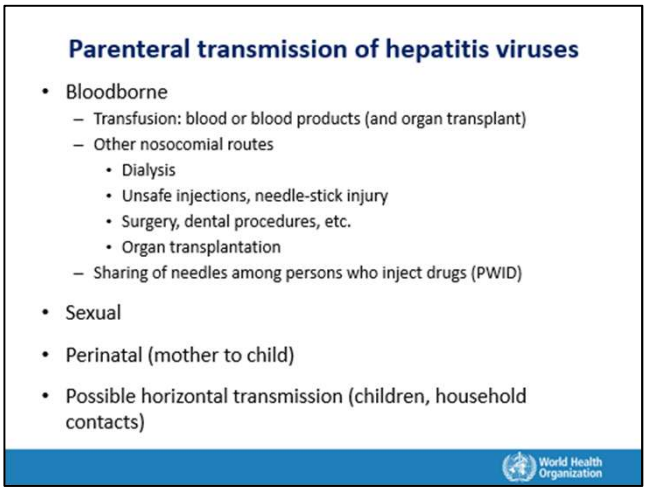
	HAV	HBV	HCV	HDV	HEV
Virus family	Picornaviridae	Hepadnaviridae	Flaviviridae	Deltaviridae	Hepeviridae
Chronicity rate	No	5% of adults 90% of infants	~75%	Co-infection of HBV; modifies course	Very rare
Hepatocellular carcinoma	No	Yes	Yes	Yes	No
Route of transmission	Person-to person Foodborne Waterborne	Perinatal Bloodborne Sexual	Bloodborne (perinatal) (sexual)	Bloodborne Sexual (perinatal)	Waterborne Foodborne Person-to-person
Vaccine	Yes	Yes	No	HBV vaccine	Not generally (licensed in China)
Treatment options	None	**Available - lifelong treatment**	**Available - CURE**	**No treatment, if HBV–HDV coinfected, treat as for HBV**	None

This slide summarizes the several clinical features of the hepatitis viruses from HAV to HEV in general. There are some differences among these viruses regarding chronicity rate, complication of hepatocellular carcinoma and routes of transmission. We shall see that only hepatitis B is a DNA virus; the rest are all RNA viruses. Hence, hepatitis B virus, akin to other DNA viruses such as CMV, HSV, etc. if it enters the human body, its DNA gets integrated with human DNA and remains inside the host body for the rest of his/her life.

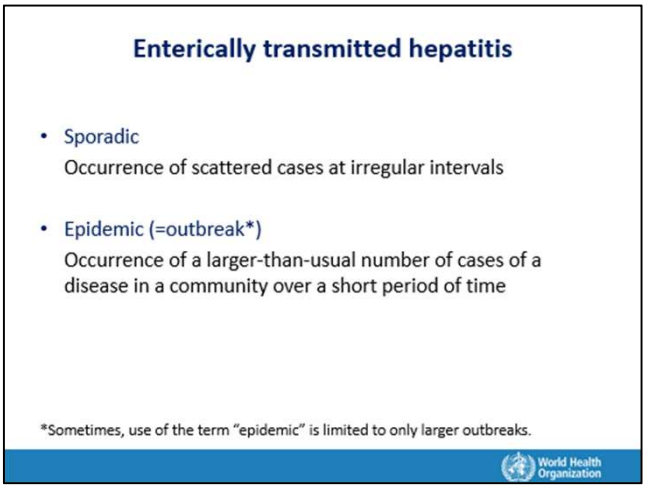


For ease of understanding, hepatitis A and E viruses can be grouped together because both of them are transmitted through the faecal–oral route by consumption of contaminated food and water; cause acute viral hepatitis and acute liver failure, and do not cause chronic viral hepatitis, liver cirrhosis or hepatocellular carcinoma. In rare cases, HEV can cause chronic hepatitis.

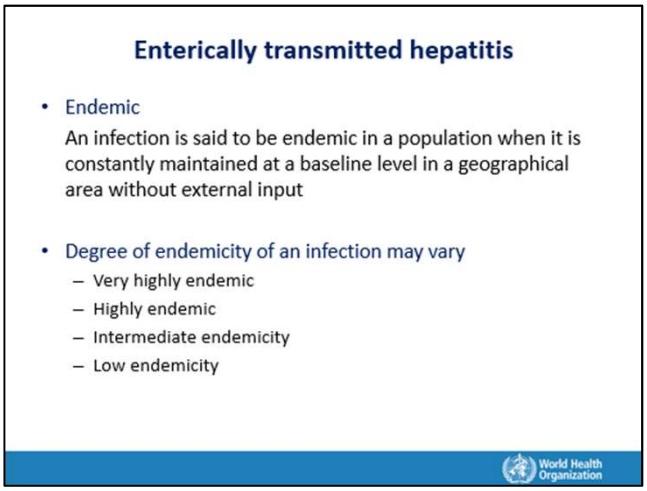
Similarly, hepatitis B, C and D can be grouped together because all of them are transmitted through the parenteral route; further, all these viruses cause chronic hepatitis, liver cirrhosis and hepatocellular carcinoma.



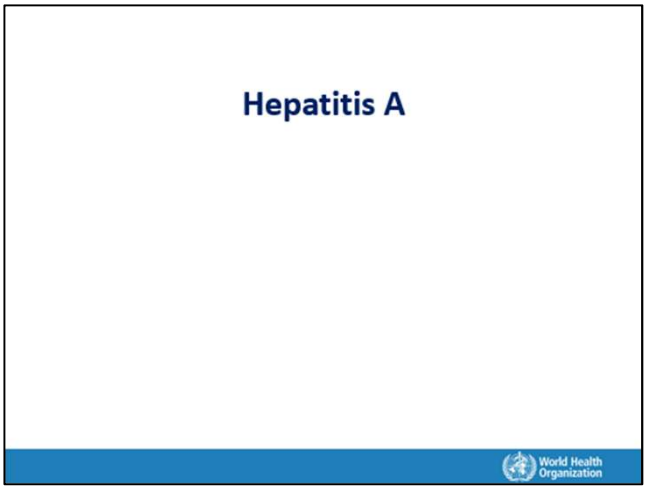
Parenteral transmission of viruses occurs following exposure through transfusion of contaminated blood or blood products, unprotected sex, in utero transmission from a pregnant woman to her baby, and possible horizontal transmission. It is important to know that hepatitis viruses can be transmitted through transfusion, dialysis, unsafe injections, needle-stick injury, surgery, dental procedures, organ transplantation or sharing of needles among persons who inject drugs because these are also interventional points.



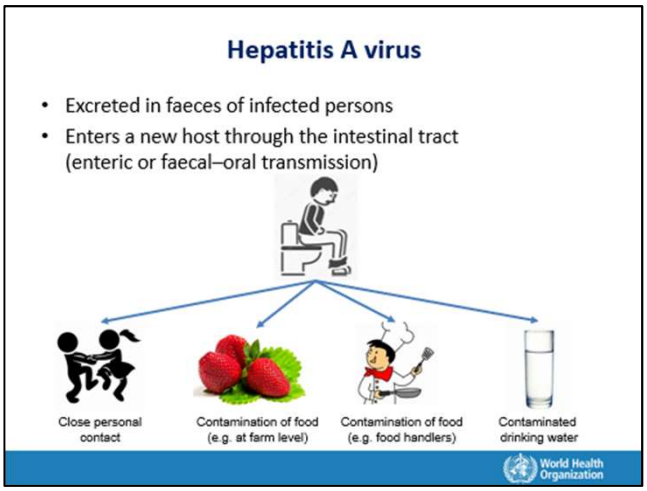
Enterically transmitted viral hepatitis could present as either sporadic hepatitis, which means the occurrence of scattered cases at irregular intervals, or in the form of an epidemic, which means the occurrence of a large number of cases of a disease in a small geographical region over a short period of time.



A health condition, specially those of infective etiology, in a geographical region is said to be endemic if it occurs commonly round the year without external input. Depending upon the disease frequency in a region, the region may be categorized as low endemic, intermediate endemic, highly endemic and very highly endemic. The cut-offs to define these endemicity categories vary from disease to disease and are not universally constant.

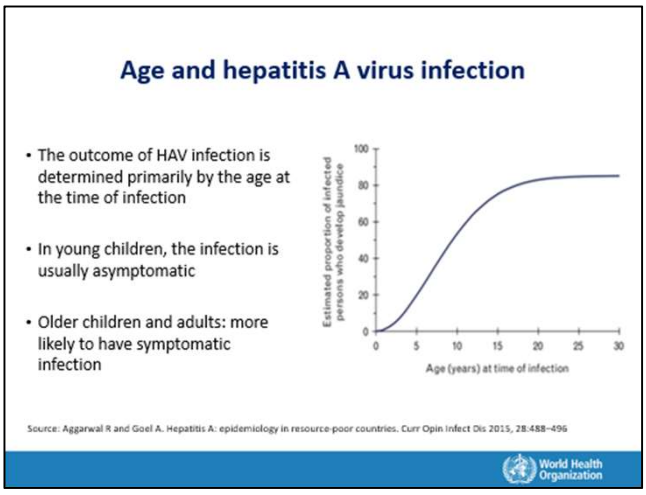


Then, please let me explain some features of each virus. At first, about hepatitis A virus.



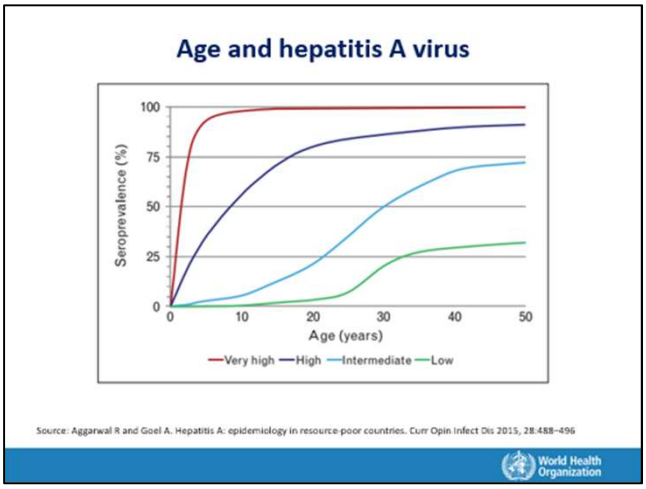
An infected person excretes hepatitis A virus in the faeces. If the water contaminated with the virus containing faeces comes in contact with food and water the virus can be transmitted to a non-infected person.

Faeces-contaminated water could come in contact with food at several points, such as during irrigation of crops, washing of raw food, contamination of drinking water because of a breach in safe water supply. Further, hepatitis A can also be transmitted from person to person by close personal contacts.



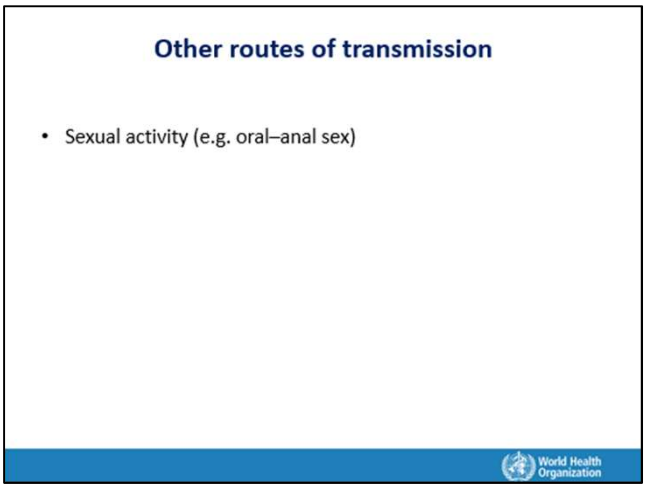
All those infected with HAV do not develop clinical illness. The majority of HAV-infected persons remain asymptomatic or develop a non-specific minor illness that usually goes unnoticed. The clinical illness is marked by the development of jaundice coupled with a marked elevation of serum levels of liver enzymes, namely, ALT and AST. The risk of developing clinical illness is primarily determined by the age of the person at the time of infection.

As the age of the host increases, the risk of clinical disease and severe illness increases. Generally, in young children, the infection is usually asymptomatic, but older children and adults have symptomatic infection.

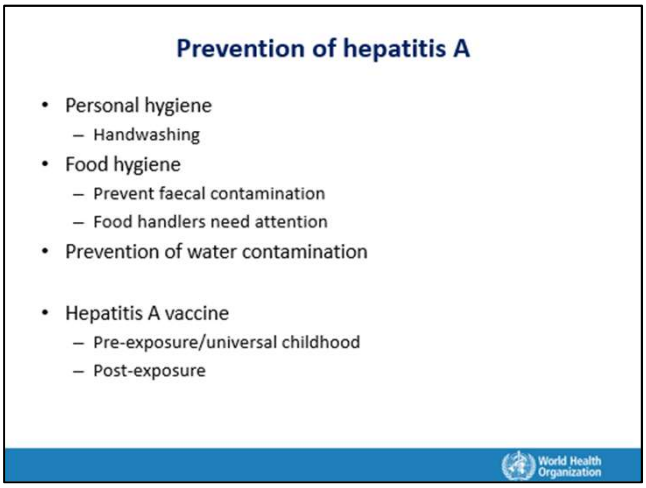


Anti-HAV antibody persists for life once it develops and hence the seroprevalence of anti-HAV antibodies keeps on increasing with age. The most likely reason for the lifelong presence of anti-HAV is repeated exposure to the virus, in particular, in those who are living in HAV-endemic countries where drinking water quality is compromised.

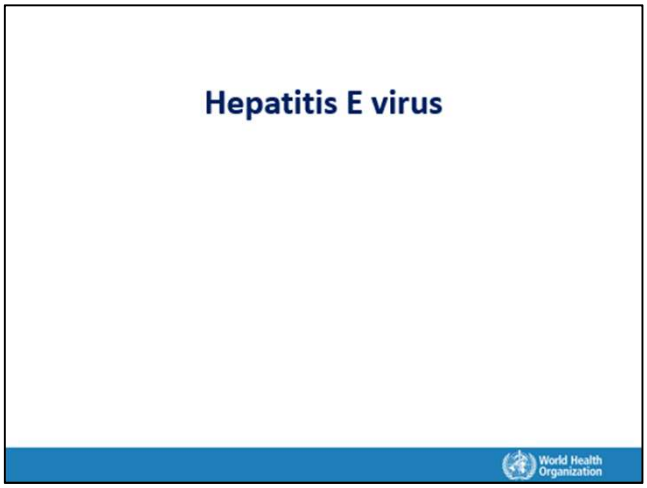
Based on the anti-HAV seroprevalence, countries in the world are divided into those with low, intermediate, high or very high endemicity. In highly endemic regions, almost 100% of children have been exposed to HAV by the age of 10 years. As we know, the majority of infections in children are asymptomatic. Hence, in highly endemic countries, the majority of infections occur in children and are not severe. In countries with low endemicity, where exposure occurs mainly in adults, clinical disease usually occurs in adults and is severe.



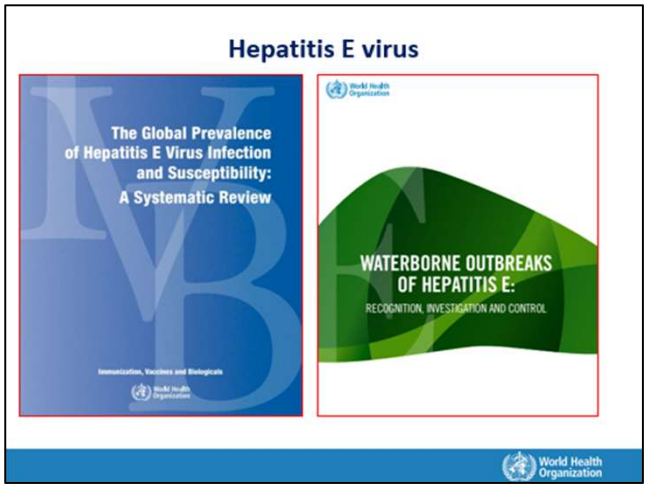
HAV can be transmitted by sexual activity. This mode of transmission is most common among adults in developed countries where endemicity of HAV infection is low. The reason for this we have just discussed in the previous slide.



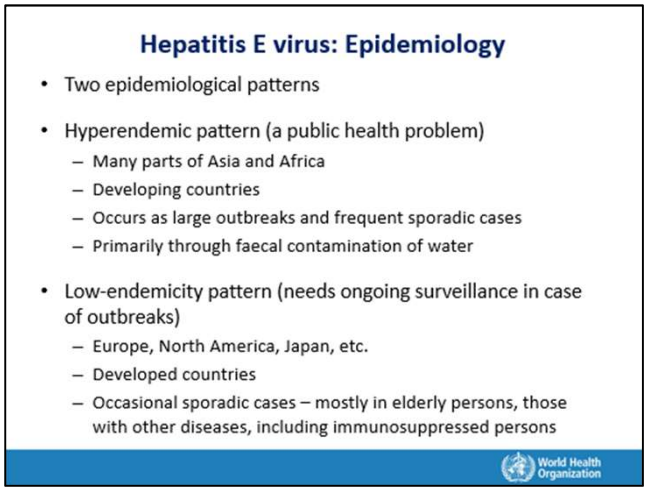
To prevent faecal–oral transmission, personal hygiene, food hygiene and prevention of water contamination is needed. Vaccination is recommended for individuals without anti-hepatitis A antibody who plan to go to a highly endemic area.



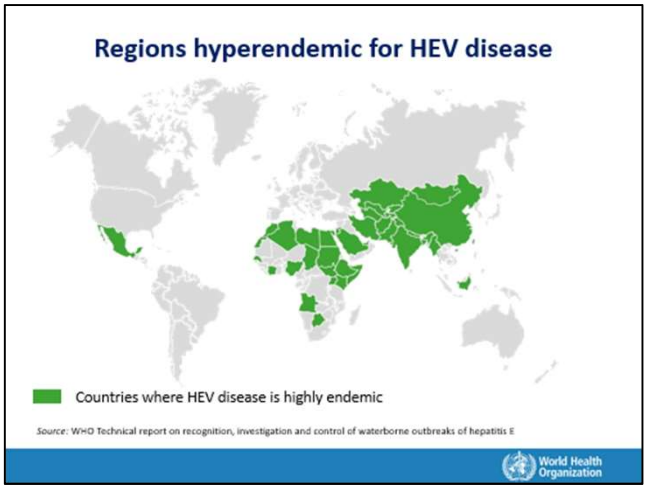
Next is hepatitis E virus, which is also transmitted through consumption of contaminated food and water.



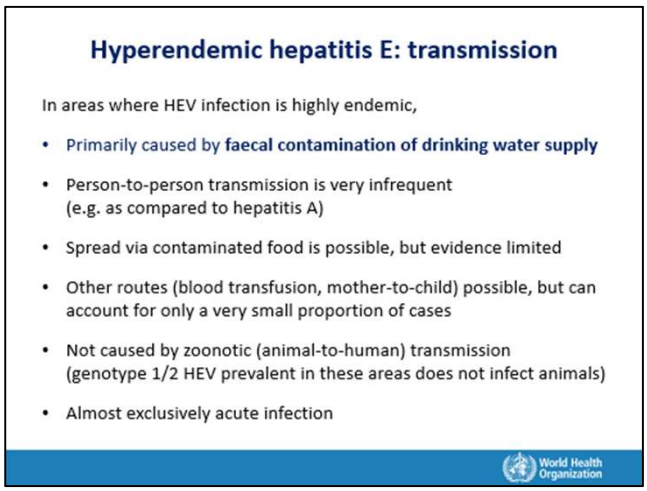
Recently, two detailed documents on hepatitis E virus infection have been published by WHO. The first one contains a comprehensive description of the seroprevalence of HEV in different countries across the world. The second one is about HEV outbreak investigation and control. HEV outbreaks are very frequent in developing countries, in particular, in south Asian countries.



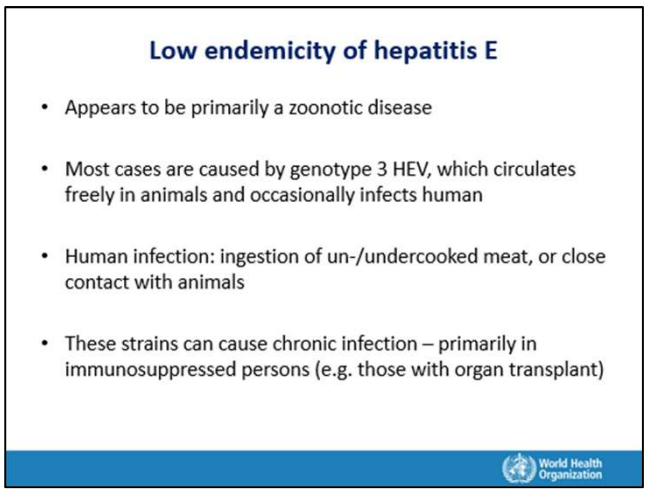
There are two epidemiological patterns of hepatitis E virus. In Asian and African countries, where HEV is hyperendemic, large outbreaks are frequent. In these regions, sporadic cases occur throughout the year. These epidemics and sporadic cases occur because of faecal contamination of the water. On the contrary, in developed countries where HEV is not endemic, only occasional sporadic cases have been seen and are primarily caused by zoonotic transmission of HEV. Ongoing surveillance is required in case of outbreaks.



In the world map shown in this slide, the green areas shows countries where HEV disease is highly endemic. Many parts of Asia and North Africa are hyperendemic zones.



In areas where HEV infection is highly endemic,
- primarily caused by faecal contamination of drinking water supply
- person-to-person transmission very infrequent (e.g. as compared to hepatitis A)
- almost exclusively acute infection



On the other hand, in areas where endemicity of HEV infection is low,
- hepatitis E virus infection appears to be primarily a zoonotic disease
- most cases are caused by genotype 3 HEV, which circulates freely in animals and occasionally infects humans
- human infection: ingestion of un-/undercooked meat, or close contact with animals
- these strains can cause chronic infection – primarily in immunosuppressed persons (e.g. those with organ transplant).

Transmission of HBV

Next is hepatitis B virus.

HBV: Routes of transmission

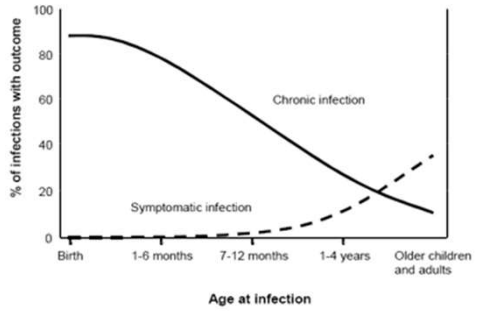
- **Perinatal: mother-to-child**
- **Horizontal: Infants/young children**, household contacts
- Health-care-associated
  - Unsafe blood and blood products
  - Unsafe injections
  - Other procedures, e.g. dental treatment
  - Needle-stick injuries
  - Organ and tissue transplantation
- Sexual (unprotected sexual intercourse)
- Sharing of syringes/needles among people who inject drugs

HBV is transmitted through the parenteral route. The most important of these are perinatal mother-to-child transmission, horizontal transmission in infants or young children in whom it leads to chronic infection, consequent cirrhosis and liver cancer.

On the other hand, horizontal transmission in older children or adults causes acute hepatitis, and most of them are asymptomatic, although in rare cases they may have fulminant hepatitis, which is fatal. More than 95% of adults with acute hepatitis B clear the virus within six months.

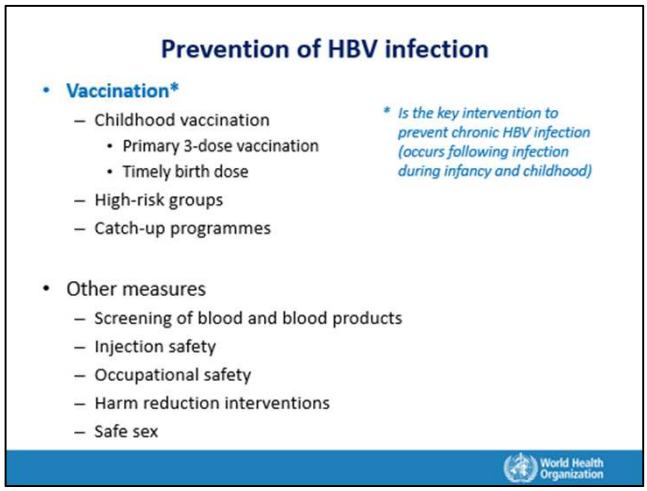
Horizontal transmission occurs in health-care-associated transmission, sexual transmission, or through sharing of syringes/needles among PWID.

HBV infection and age at acquisition



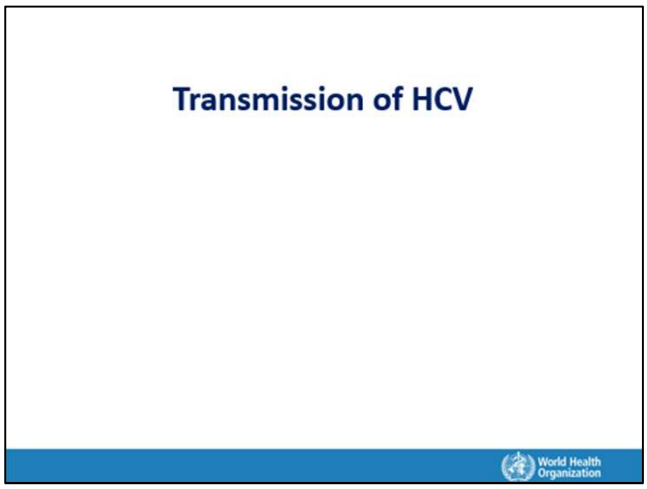
Infections during infancy and early childhood are particularly likely to lead to chronic infection, with the risk of cirrhosis and death (a public health problem)

The natural history of HBV infection depends upon the age of the host at the time of infection. There is an inverse relationship between the risk of developing acute hepatitis and its progression to chronic infection and the age of the host. Infections during infancy remain asymptomatic and carry more than 90% chance of progressing to chronic infection. By the age of 5 years, about 20% develop chronic infection. After the age of 5 years and particularly in adults, more than 90% develop acute hepatitis and clear the virus within six months.



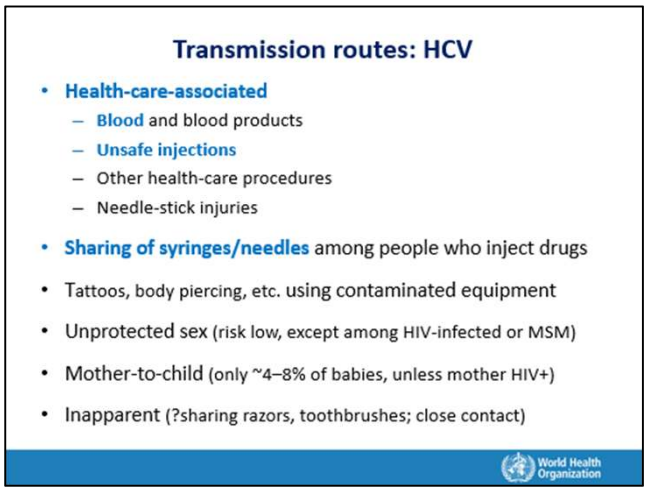
Because the majority of chronic HBV infections occur following infection during infancy and childhood,

- Vaccination is the key intervention to prevent chronic HBV infection.
- Adequate coverage of hepatitis B vaccination could be achieved through birth dose vaccination, routine childhood vaccination, vaccination of high-risk groups, and catch-up programmes to vaccinate susceptible adults. Among the various strategies for hepatitis B vaccination, childhood vaccination is the most important because children are at the maximum risk of developing chronic infection and also have the longest period of risk of developing the complications of chronic HBV infection such as cirrhosis or liver cancer.
- Other prevention measures are screening of blood and blood products, injection safety, occupational safety, harm reduction interventions and safe sex, etc.

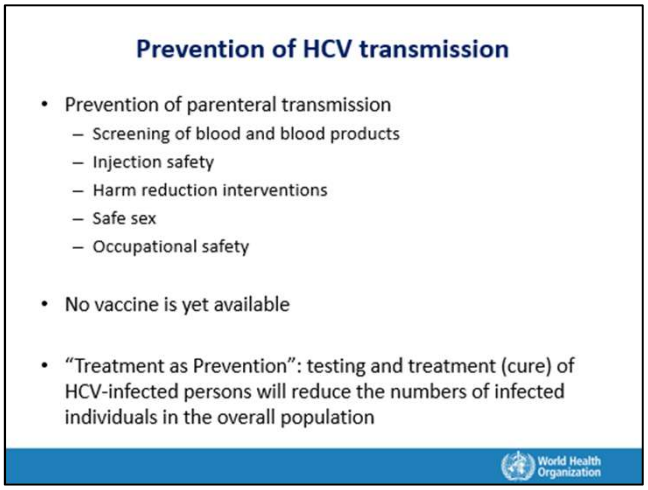


Another hepatotropic virus which is transmitted through the parenteral route.

In the past few years, the treatment of HCV infection has seen a major change in terms of efficacy, safety, cost and ease of administration. Actually, it is the recent game change in HCV treatment which has led to the enhanced global response against viral hepatitis.



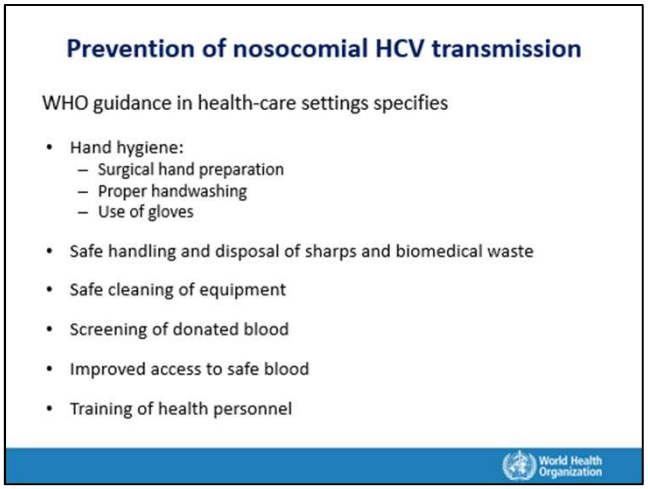
HCV infection also has several transmission routes. Similar to HBV, the main routes of HCV transmission are health-care activities such as blood transfusion, unsafe injections, needle-stick injuries or other healthcare procedures. As well as HBV, sharing of syringes/needles among PWID, unprotected sex, mother-to-child transmission also can cause HCV transmission.



There is no vaccine

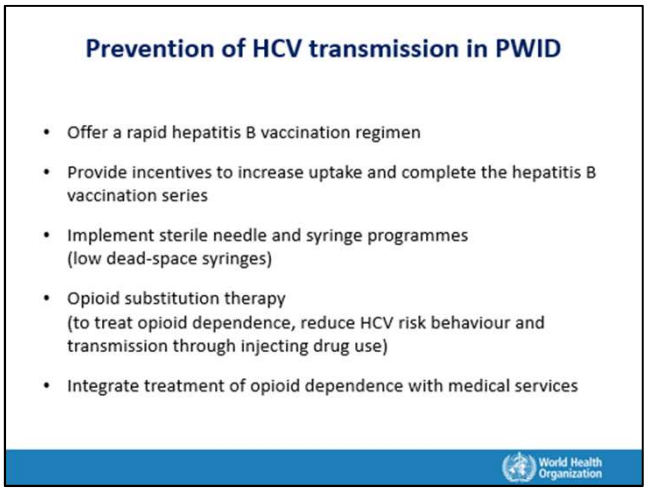
As a way of preventing parenteral transmission mainly to health-care providers, it is important to do the following:

- Screening of blood and blood products
- Injection safety
- Harm reduction interventions
- Safe sex
- Occupational safety.



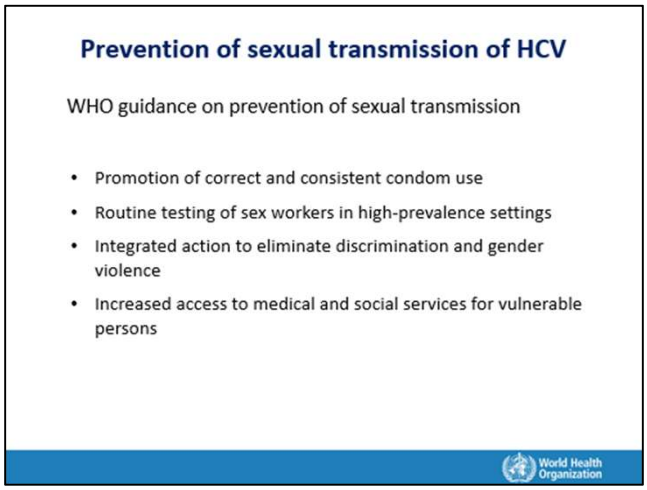
To prevent nosocomial HCV transmission, WHO guidance recommended

- Hand hygiene:
  - ✓ Surgical hand preparation
  - ✓ Proper handwashing
  - ✓ Use of gloves
- Safe handling and disposal of sharps and biomedical waste
- Safe cleaning of equipment
- Screening of donated blood
- Improved access to safe blood
- Training of health personnel

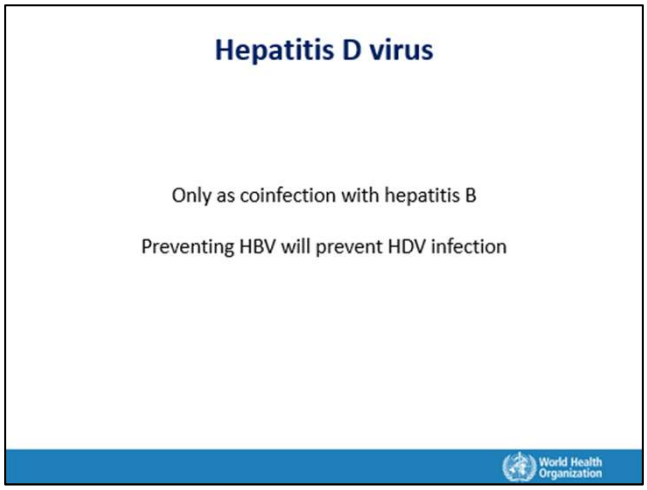


To prevent HCV transmission in PWID,

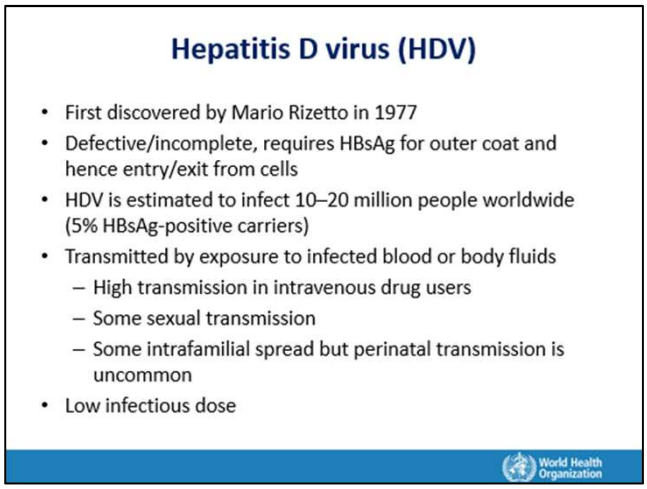
- Offer a rapid hepatitis B vaccination regimen
- Provide incentives to increase uptake and complete the hepatitis B vaccination series
- Implement sterile needle and syringe programmes (low dead-space syringes)
- Opioid substitution therapy (to treat opioid dependence, reduce HCV risk behaviour and transmission through injecting drug use)
- Integrate treatment of opioid dependence with medical services



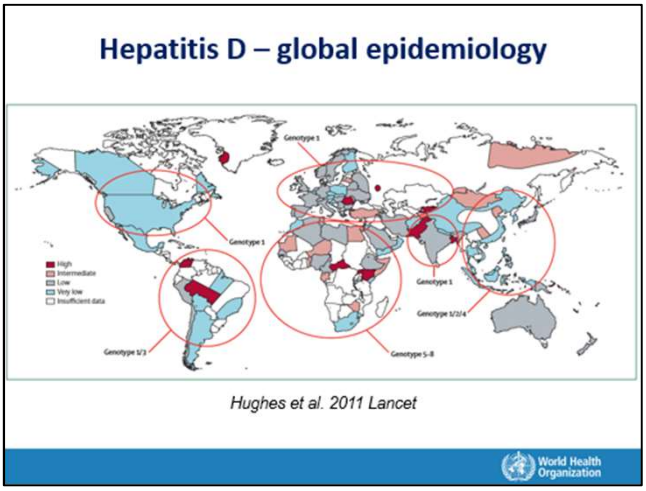
To prevent sexual transmission of HCV
- Promotion of correct and consistent condom use
- Routine testing of sex workers in high-prevalence settings
- Integrated action to eliminate discrimination and gender violence
- Increased access to medical and social services for vulnerable persons



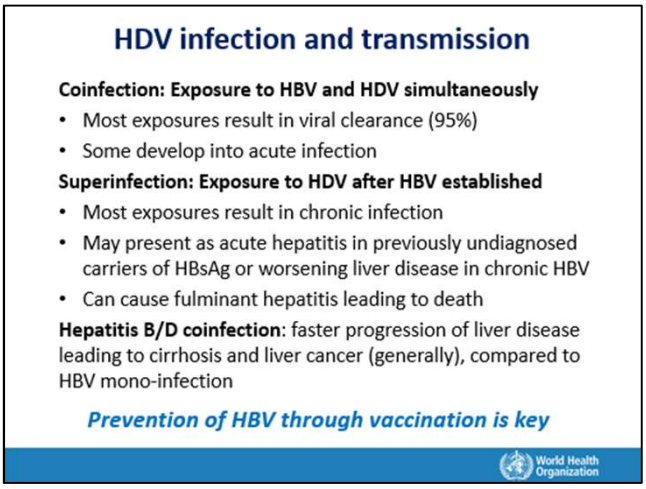
The last hepatitis virus is hepatitis D virus. HDV infection is established only as a coinfection with hepatitis B. If we can prevent transmission of HBV, we can also prevent HBV infection.



This slide provides general information about HDV.
- HDV was first discovered by Mario Rizetto in 1977
- Defective/incomplete, requires HBsAg for outer coat and hence entry/exit from cells
- HDV is estimated to infect 10–20 million people worldwide (5% HBsAg-positive carriers)
- Transmitted by exposure to infected blood or body fluids
  - High transmission in intravenous drug users
  - Some sexual transmission
  - Some intrafamilial spread but perinatal transmission is uncommon
- Low infectious dose



This slide shows the distribution of hepatitis D virus. You can see that some areas of the Western Pacific Region have intermediate endemicity.

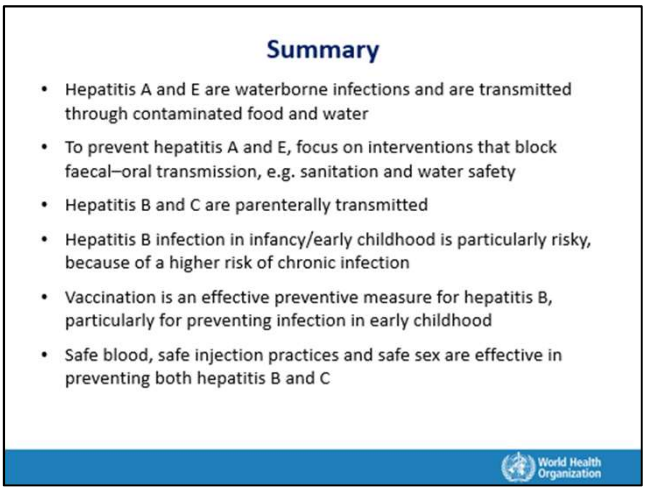


There are two patterns of HBV and HDV infection.

One is coinfection in those exposed to HBV and HDV simultaneously. This form of transmission can cause acute hepatitis but mostly results in viral clearance.

Another is superinfection, in which patients with chronic HBV infection or HBV carriers are exposed to HDV. This way of transmission can cause fulminant hepatitis leading to death.

It is important to know that hepatitis B and D coinfection leads to faster progression of liver disease to cirrhosis and liver cancer compared to HBV mono-infection. Whatever the infection patterns, prevention of HBV through vaccination is key to preventing HDV infection.



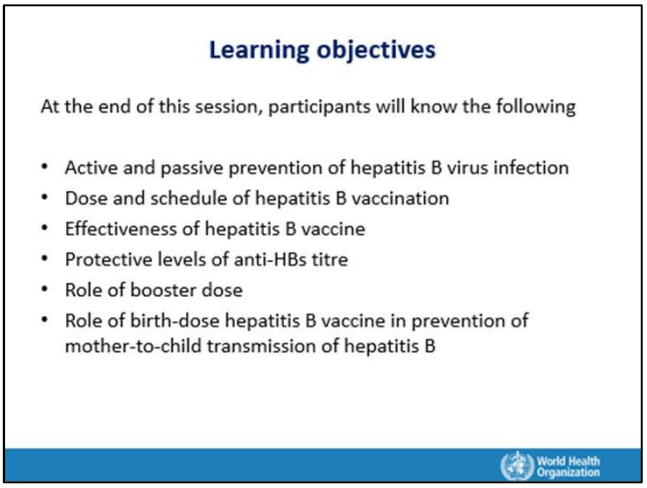
In summary,

- Hepatitis A and E are waterborne infections and are transmitted through contaminated food and water
  - ✓ To prevent hepatitis A and E, focus on interventions that block faecal–oral transmission, e.g. sanitation and water safety
- Hepatitis B, C and D are parenterally transmitted
  - ✓ Hepatitis B infection in infancy/early childhood is particularly risky, because of a higher risk of chronic infection
  - ✓ Hepatitis D only occurs if a person has hepatitis B.
- Vaccination is an effective preventive measure for hepatitis B, particularly for preventing infection in early childhood
- Safe blood, safe injection practices and safe sex are effective in preventing both hepatitis B and C.

Module 6

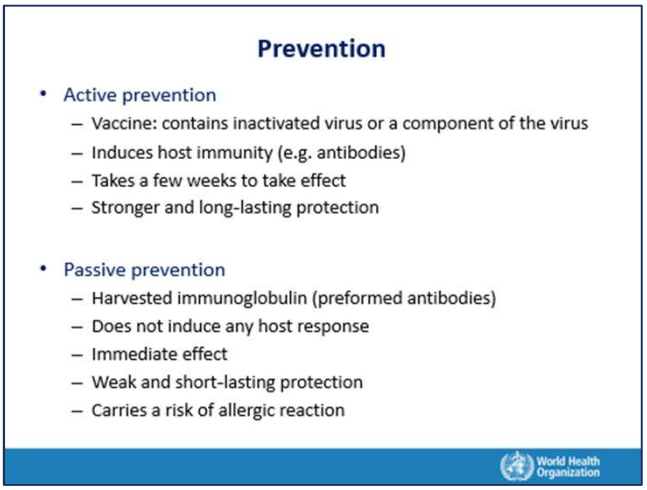
Hepatitis B vaccination and prevention of mother-to-child transmission (PMTCT)

Module 6



At the end of this session, participants will understand the following

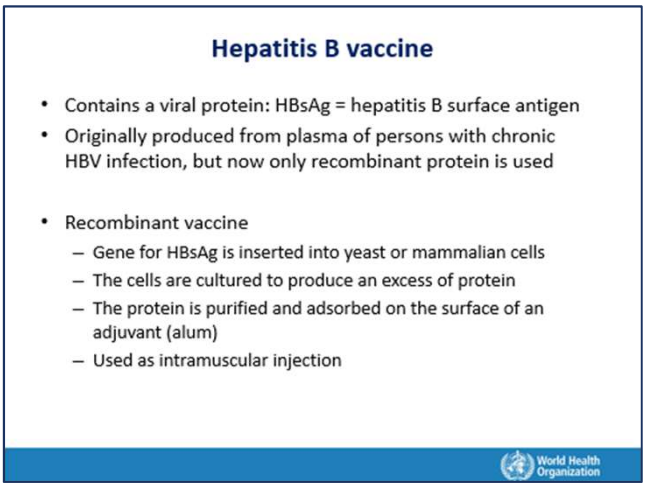
- Active and passive prevention of hepatitis B virus infection
- Dose and schedule of hepatitis B vaccination
- Effectiveness of hepatitis B vaccine
- Protective levels of anti-HBs titre
- Role of booster dose
- Role of birth-dose hepatitis B vaccine in prevention of mother-to-child transmission of hepatitis B
- Evolving new evidence, strategy and guidance in HBV prevention and control



In general, there are two ways to prevent HBV infection: the first is active prevention; and second is passive prevention.

Active prevention is provided by the vaccine, which contains inactivated virus or a component of the virus. Vaccination induces host immunity and enables stronger and long-lasting protection, but it takes a few weeks to take effect.

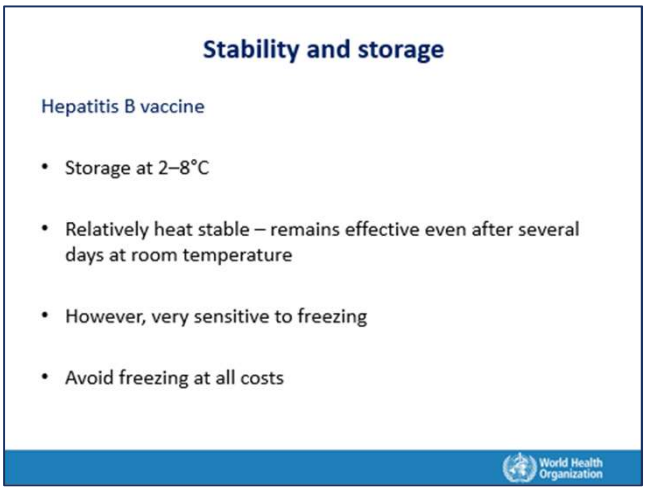
On the other hand, passive prevention is induced by administration of harvested immunoglobulin. Immunoglobulin does not induced any host response, and its effect is weaker and shorter than that of the vaccine. However, it works immediately after administration. Because of homogeneous harvesting, immunoglobulin carries a risk of an allergic reaction.



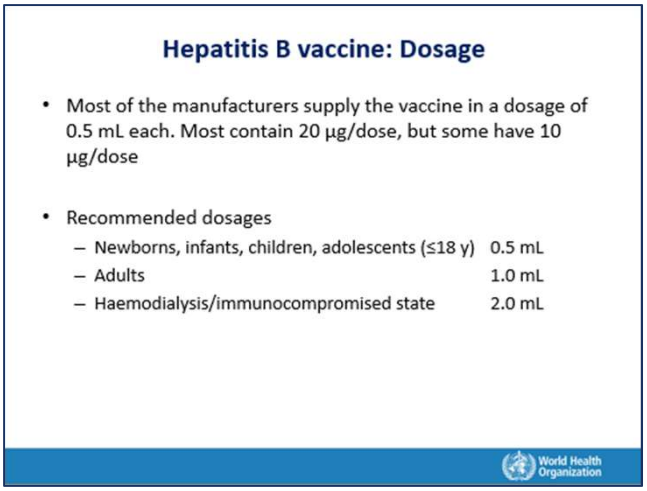
We need to spend some time while discussing hepatitis B vaccine to understand it well.

Hepatitis B vaccine contains a viral protein of hepatitis B surface antigen - originally produced from the plasma of persons with chronic HBV infection, but now only recombinant protein is used. Recombinant vaccine is prepared as follows.

Gene for HBsAg is inserted into yeast or mammalian cells.
The cells are cultured to produce an excess of protein.
The protein is purified and adsorbed on the surface of an adjuvant (alum).
Finally, it is used as an intramuscular injection.



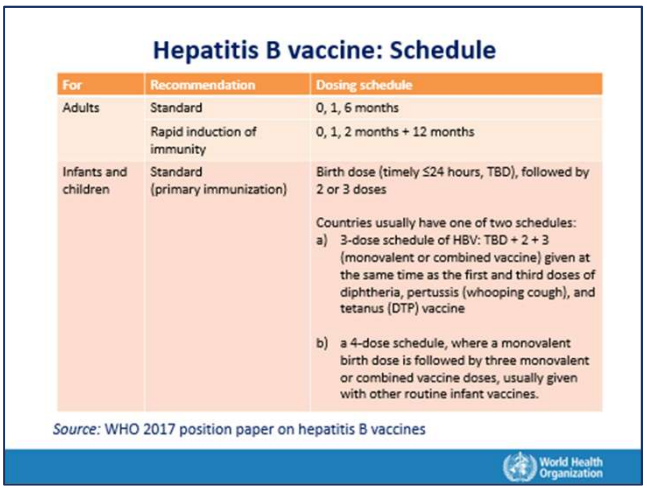
- About the stability and storage, it is recommended that hepatitis B vaccine be stored at 2–8℃.
- Relatively heat stable – remains effective even after several days at room temperature
- However, the vaccine is very sensitive to freezing, and you must avoid freezing at all costs.



Most of the manufactures supply the vaccine in a dosage of 0.5 mL containing 20 µg/dose, but we must pay attention to the dose because some have 10 µg/dose.

Recommended dosages are as follows:
Newborns, infants, children, and adolescents at 18 years of age or younger 0.5 mL

Dosage of adults is 1.0 mL
Dosage for adults on haemodialysis or immunocompromised hosts is 2.0 mL



We need to administer at least 3 doses of the vaccine to infants for sufficient efficacy. It should be made clear to health workers that the birth dose, which is given within 24 hours of birth, is in addition to the routine three-dose vaccination.

Global Health Sector Strategy on Viral Hepatitis

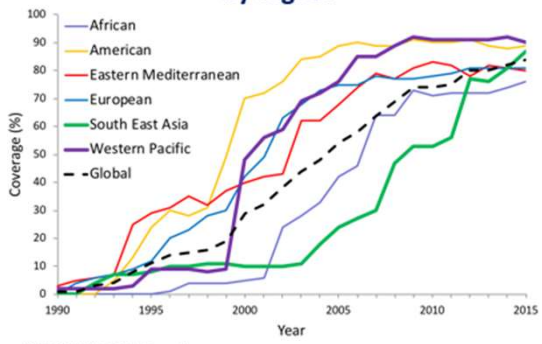
Type of target	Intervention	Western Pacific Region, 2015	South-East Asia Region, 2015	2020 target	2030 target
Service coverage	3-dose hepatitis B vaccine	93% (2016)	87%	90%	90%
	HBV PMTCT	83% (2016)	34%	50%	90%
	Blood safety (% donations screened)	98%	85%	95%	100%
	Injection safety (% unsafe injections)	3.2%	5.2%	0%	0%
	Harm reduction (injection sets/PWID)	57	29	200	300
Impact	HBV incidence: HBsAg +ve in 5 year old)	0.93% (2016)	0.7% (2015)	–30% (~1%)	–90% (0.1%)
	HCV incidence	6 per 100 000	14.8 per 100 000	–30%	–90%

PMTCT: prevention of mother-to-child transmission (universal birth dose or other approaches)
PWID: person who injects drugs
Source: Global Hepatitis Progress 2017

World Health Organization

Coverage with three doses of hepatitis B vaccine is one of the WHO targets (90%) by 2030.

Infant HBV vaccine coverage (3 doses): by region

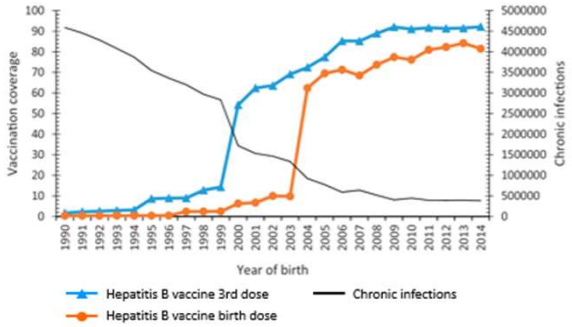


Source: WHO AND UNICEF Joint Reporting

World Health Organization

The global coverage of hepatitis B vaccination has seen major progress since 2000. About 84% of infants were vaccinated with three doses of hepatitis B vaccine in 2015. WPR had an estimated 90% coverage in 2015 and 93% in 2016.

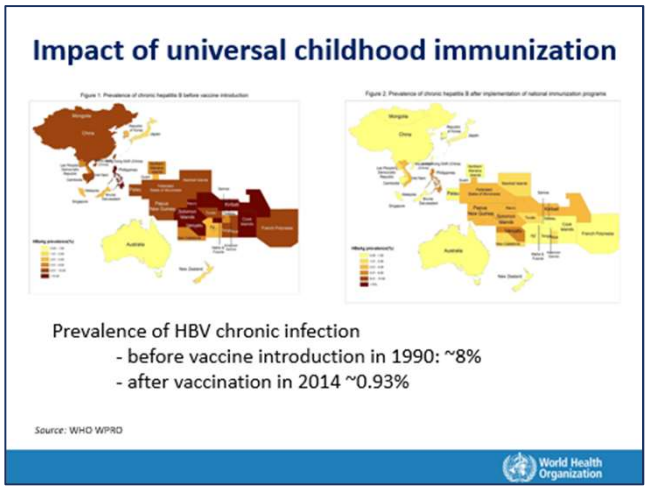
Impact of vaccine coverage (WPR) on HBV rate



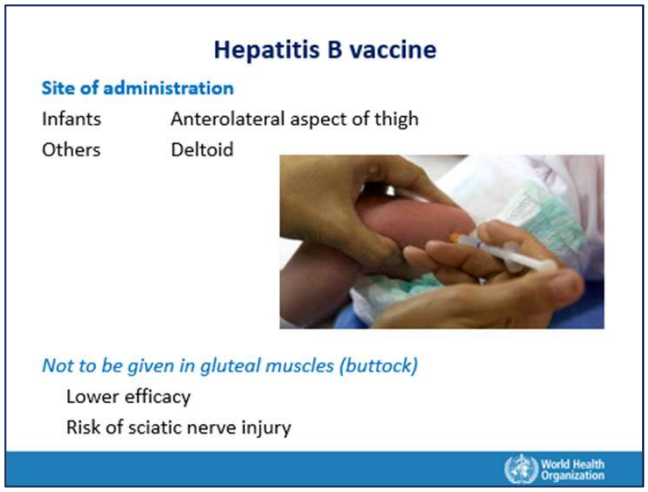
Source: Eric Wiesen et al., Progress towards hepatitis B prevention through vaccination in the Western Pacific, 1990-2014. Vaccine 2016

World Health Organization

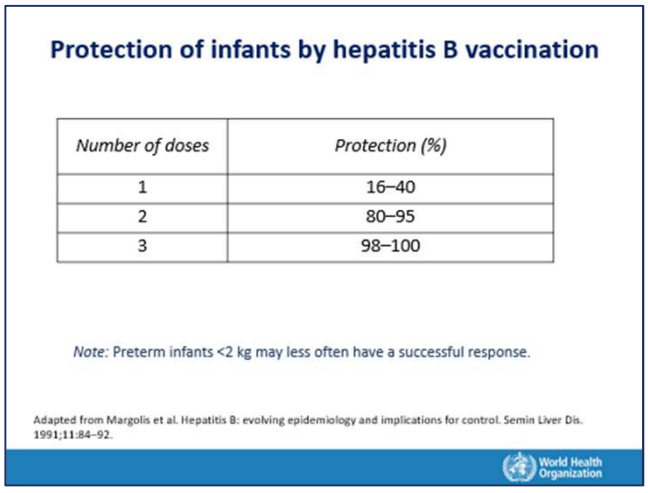
In WPR, coverage with the birth dose of hepatitis B vaccine has been slightly lower than that of the 3rd dose of hepatitis B vaccine. Birth dose vaccination coverage has reached around 80% in WPR.



The slide shows the impact of universal childhood hepatitis B vaccination on the prevalence of chronic hepatitis B in 22 of 36 countries where the vaccine was introduced in 1990. In these countries, the HBV prevalence before the introduction of vaccination was 8%, which has dramatically reduced to below 1% after the successful implementation of universal childhood hepatitis B vaccination.



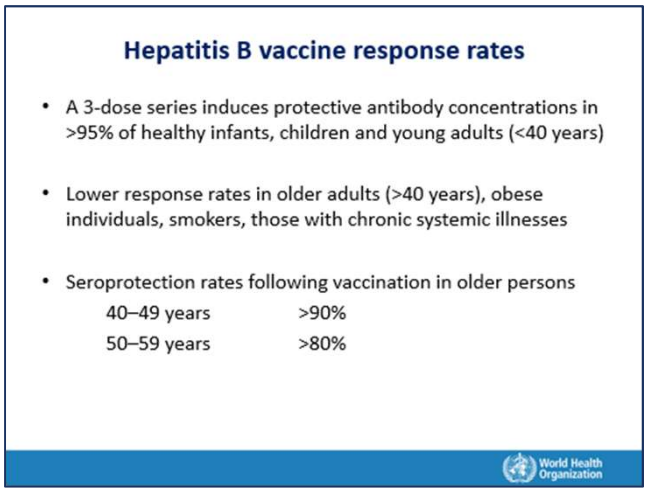
We should administer HBV vaccine intramuscularly on the anterolateral aspect of the thigh in infants and deltoid for others. We must not administer HBV vaccine in the gluteal muscles because vaccination at this has been shown to have lower efficacy and a definitive risk of sciatic nerve injury.



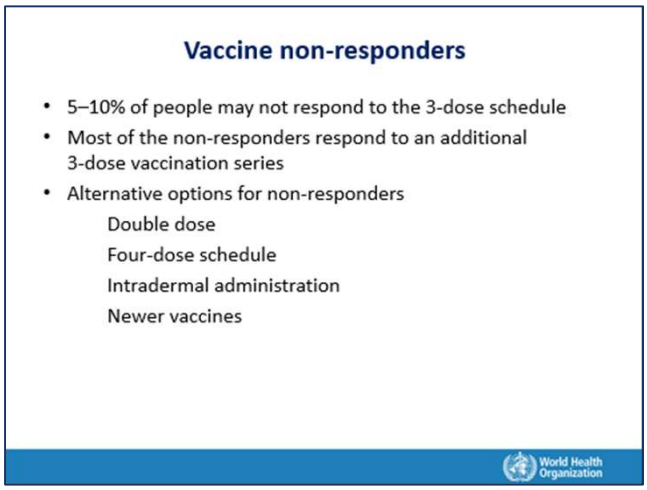
The efficacy of hepatitis B vaccine is defined by the presence of an anti-HBs antibody titre of 10 mIU/mL or higher. The proportion of infants that achieves this protective level of anti-HBs titre after one, two or three doses of the vaccine gradually increases.

Even a single dose of vaccine induces a small degree of protective immunity, which ranges from 16% to 40%.

The second dose markedly enhances the proportion of children developing protective immunity. The third dose of the vaccine works more like a booster dose and it has three effects: first, it slightly increases the proportion of children that develop protective immunity to 95%; second, it increases the level of antibody titre in those who develop immunity; and third, it better sustains the antibody titre.



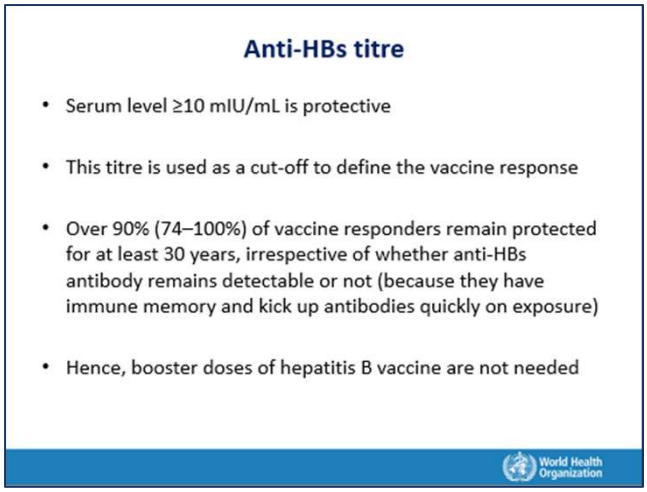
A 3-dose series induces protective antibody concentrations in >95% of healthy infants, children and young adults (<40 years). Lower response rates are seen in older adults (>40 years), obese individuals, smokers and those with chronic systemic illnesses .



Though we have highly potent hepatitis B vaccine available with us, about 5–10% of people may not respond to the 3-dose schedule and they are called vaccine non-responders.

We have a few alternatives for these non-responders, such as the following:

- About 50% of non-responders may respond to an additional 3-dose vaccination series.
- Alternative options for non-responders are
  - repeating the three- or four-dose schedule using double the usual dose
  - administering the vaccine intradermally
  - using experimental newer vaccines



- As discussed earlier, the protective efficacy of hepatitis B vaccine is assessed by the serum levels of anti-HBs antibody titre.
- In general, serum anti-HBs level ≥10 mIU/mL is considered to be protective.
- It is important to mention that, once the anti-HBs titre has reached the protective level, over 90% of individuals will remain protected for over 20 years, irrespective of whether the anti-HBs antibody remains detectable or not.
- WHO does not recommend either booster vaccination after the 3-dose vaccination schedule or repeated anti-HBs titre estimation once its protective level has been achieved.

HBV vaccines: Adverse events

Nature of adverse event	Description	Frequency (rate / doses)
Mild	Local reactions	
	Pain	3–29 per 100
	Erythema	3 per 100
	Swelling	3 per 100
	Generalized reactions	
	Temperature >37.7°C	1–6 per 100
	Headache	3 per 100
Severe	Anaphylaxis	1.1 per million

World Health Organization

Mild adverse events of HBV vaccine have been reported at a low frequency . Overall, hepatitis B vaccine is extremely safe and serious adverse effects are very uncommon.

HBV vaccine: Other considerations

- A subunit vaccine (no live virus). Hence, safe even in persons with immunodeficiency
- No mutual interference when co-administered with other childhood or adult vaccines

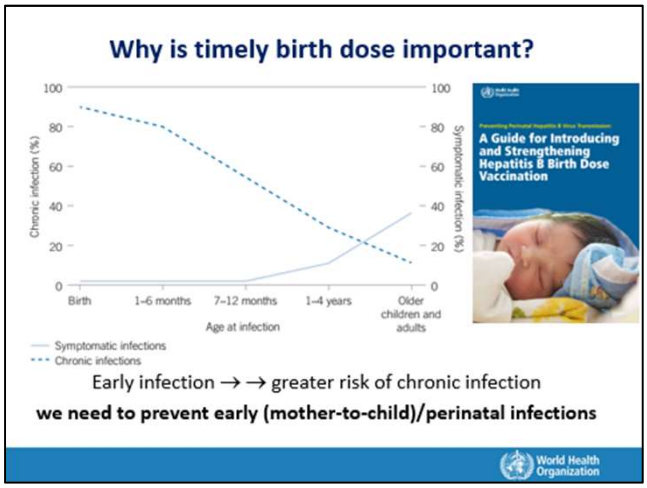
World Health Organization

Currently used hepatitis B vaccines are subunit vaccines and hence they are safe in high-risk populations such as immunocompromised people, low-birth-weight baby, and preterm babies. There is no mutual interference on co-administration with other childhood or adult vaccines.

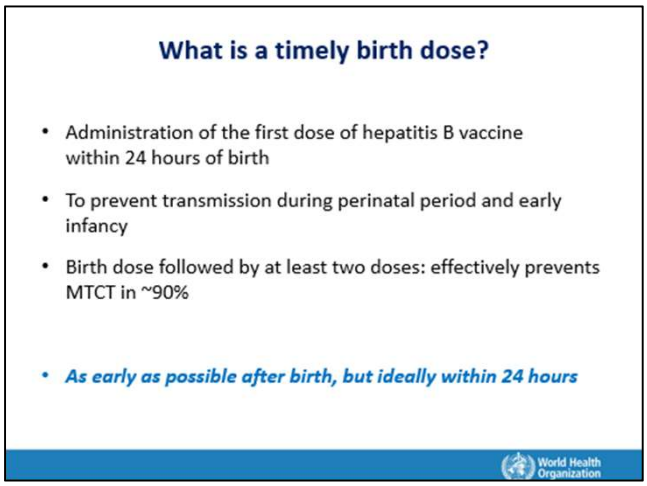
Birth dose and mother-to-child transmission (MTCT)

World Health Organization

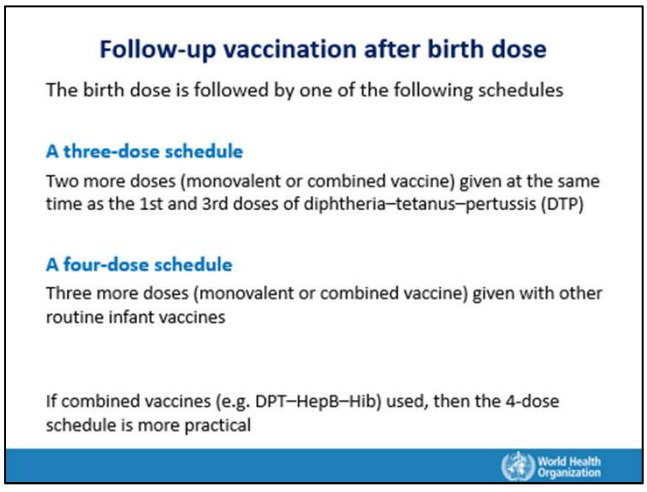
In this section we will learn about the method of preventing mother-to-child transmission of hepatitis B, which is one of the most common routes of hepatitis B transmission in developing countries in Asia and Africa.



The natural history of HBV infection depends upon the age of the host at the time of infection. There is an inverse relationship between the risk of developing acute hepatitis and its progression to chronic infection and the age of the host. Infections during infancy remain asymptomatic and carry more than 90% chance of progressing to chronic infection. By the age of 5 years, about 20% develop chronic infection. After the age of 5 years and particularly in adults, more than 90% develop acute hepatitis and clear the virus within six months.



WHO recommends a timely birth dose within 24hours of birth. As far as possible, all birth doses should be given within 24 hours of delivery but if birth dose administration delayed, due to any reason, it should NOT be refused. This message should be passed on to health-care workers. This dose is given in addition to the routine vaccination schedule.



The birth dose of HBV should not be counted as a the first dose of the routine childhood vaccination schedule prevailing in the country. Rather, the birth dose should be considered as an extra dose administered in addition to the routine vaccination schedule.

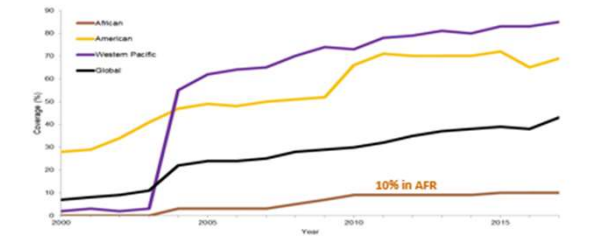
Birth dose coverage

- WHO advocated for universal administration of hepatitis B birth dose in 2009
- Globally, the birth dose coverage was 38% in 2014 and 43% in 2017, with wide variability among countries and regions

World Health Organization

Coverage of hepatitis B birth dose, 2017

- From 38% in 2015 to 43% coverage in 2017



No progress	Incomplete, minor actions	Incomplete, but major actions	On track, gaps	On track, minor gaps

Source: WHO AND UNICEF Joint Reporting

World Health Organization

That other intervention is the birth dose. On the slide, you can see the coverage of the birth dose of hepatitis B vaccine between 2000 and 2015 for selected regions. We have had success stories in the Western Pacific region where perinatal transmission was a major problem. In the Americas, coverage tremendously increased also. However, global coverage (as a dashed black line) is still low at 39% and in the African region which is highly endemic for hepatitis B, the coverage of the timely birth dose is only 10%.

Mother-to-child transmission (MTCT)

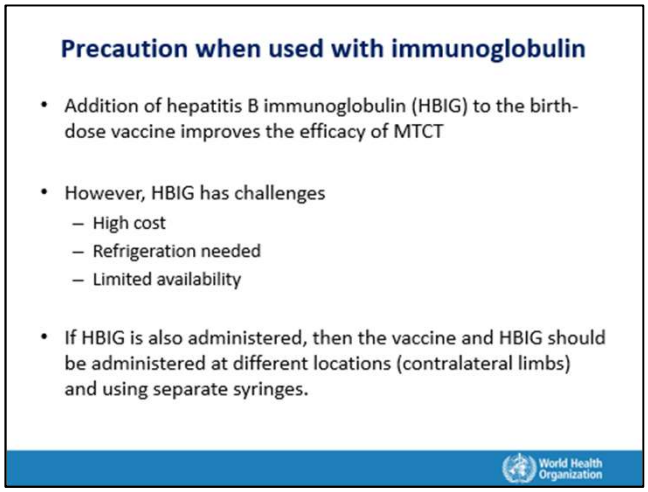
In many endemic countries, the majority of the HBV burden is related to mother-to-child transmission at birth or due to other exposure during early infancy

- High birth rates
- Poor antenatal care
- Poor birth hygiene
- Poor coverage of hepatitis B birth dose
- High population density
- Excess use of injections for minor childhood illnesses

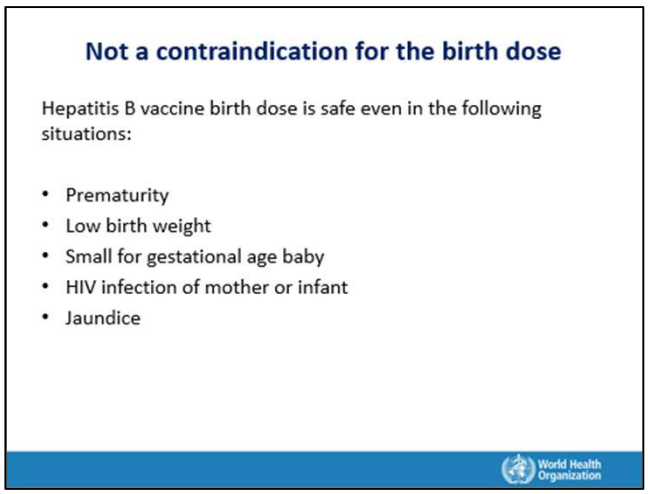
Birth dose helps to better prevent such early (chronic) infections.

World Health Organization

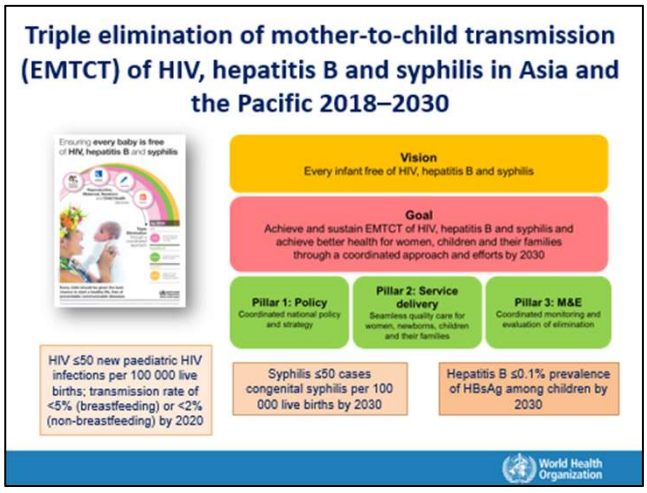
In several resource-poor countries, HBV is transmitted during infancy. This transmission happens either from the mother or from the surroundings due to the reasons mentioned above. The birth dose is effective in preventing HBV infection during infancy.



At many places, HBIG is also administered as a part of the HBV prophylaxis strategy to prevent MTCT. We must know that in a public health setting, HBIG is costly, needs timely administration and facilities for storage and transport. The benefits of the additional use of HBIG is limited. If HBIG and HBV vaccine are both given; they should be given simultaneously intramuscularly in different thighs.

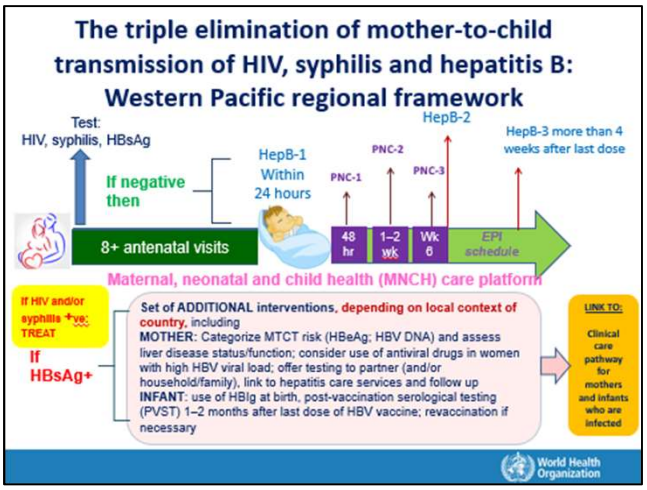


HBV vaccine has been shown to be effective and safe in the above-mentioned high-risk group babies.

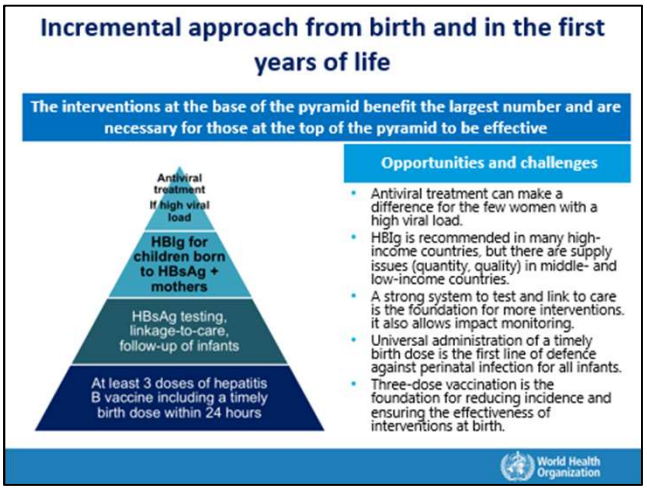


The triple elimination framework has a clear vision, goals and targets to be achieved. This framework piggybacks on the existing dual elimination, with HBV elimination added on. The ultimate target for HBV elimination is 0.1% prevalence among children by 2030.

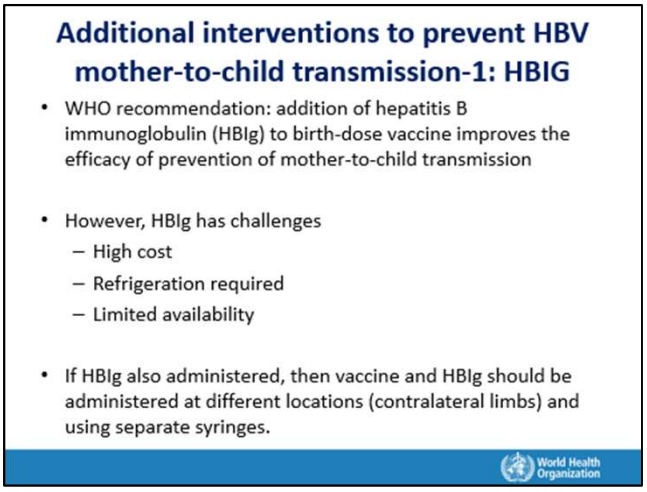
Module 6



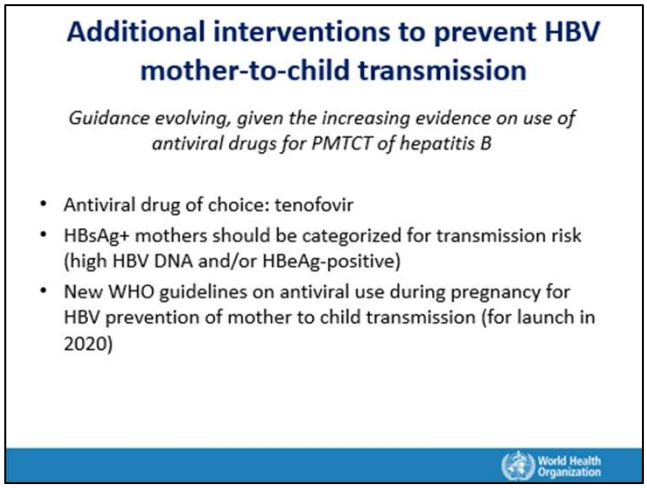
In pragmatic terms, using the maternal neonatal and child health care platform, universal testing for HIV, syphilis and hepatitis is offered. If positive, interventions are provided. For HBV-positive pregnant women, a set of additional interventions can include antiviral drug use for prevention of mother-to-child transmission, and among infants, post-vaccination serological testing to know their infection status.



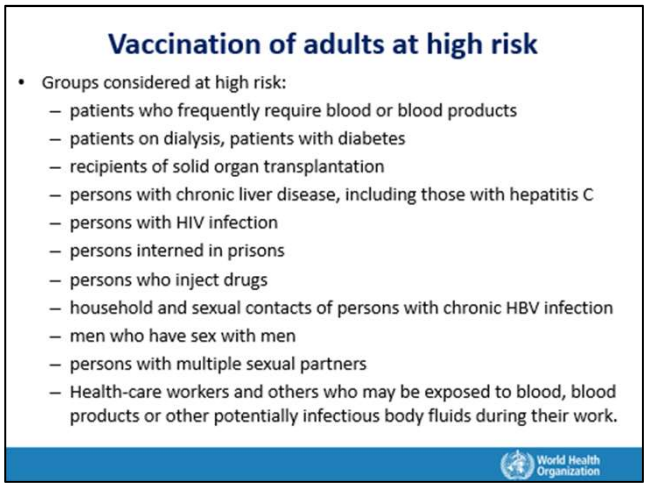
Taking the incremental approach, and building from the foundation of the immunization programme, work upwards through improving access to testing, linkage to care and follow up, and antiviral drug use for women who have a high viral load – so as to work towards an “almost zero infection” status



WHO also recommends that addition of hepatitis B immunoglobulin to birth-dose vaccine improves the efficacy of prevention of mother-to-child transmission. However, HBIg has some challenges, including high cost, need for refrigeration and limited availability. If HBIg is available, the vaccine and HBIg should be given at the same time but at different sites using separate syringes.

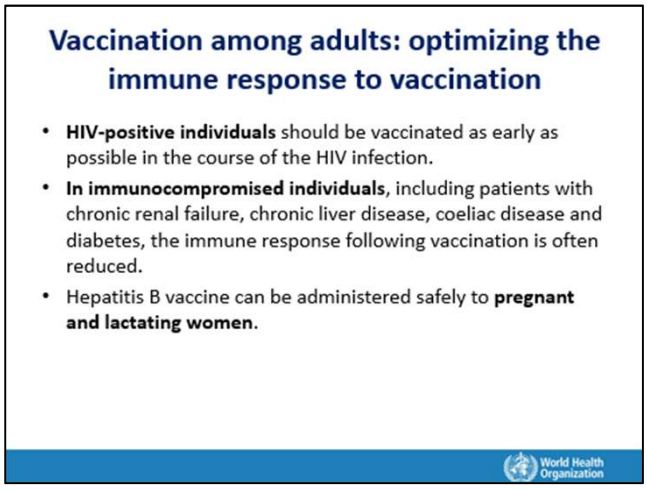


Another additional intervention is antiviral drugs. It has been reported that the transmission rate of HBV was suppressed by the administration of tenofovir to high-risk women with HBeAg positivity and high viral load of HBV. Although there are some ongoing discussion points, antiviral drugs may become a useful option for PMTCT of HBV, given the increasing evidence.



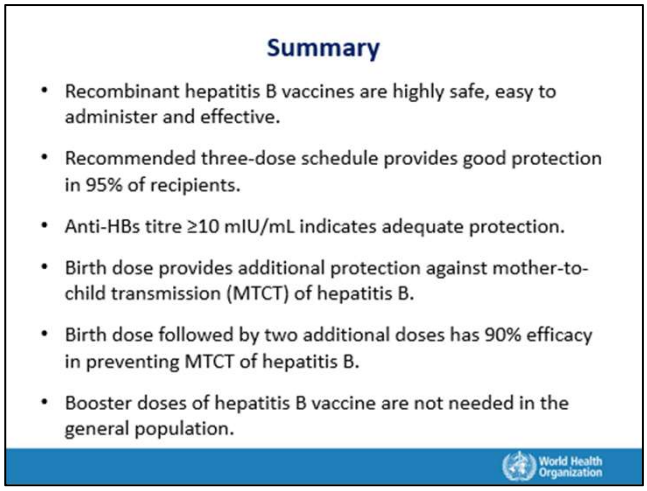
WHO also recommends vaccination for adults at high risk such as the following:.

- patients who frequently require blood or blood products
- Patients on dialysis, patients with diabetes
- recipients of solid organ transplantation
- persons with chronic liver disease, including those with hepatitis C
- persons with HIV infection
- persons interned in prisons
- persons who inject drugs
- household and sexual contacts of persons with chronic HBV infection
- men who have sex with men
- persons with multiple sexual partners
- Health-care workers and others who may be exposed to blood, blood products or other potentially infectious body fluids during their work.



Among them,

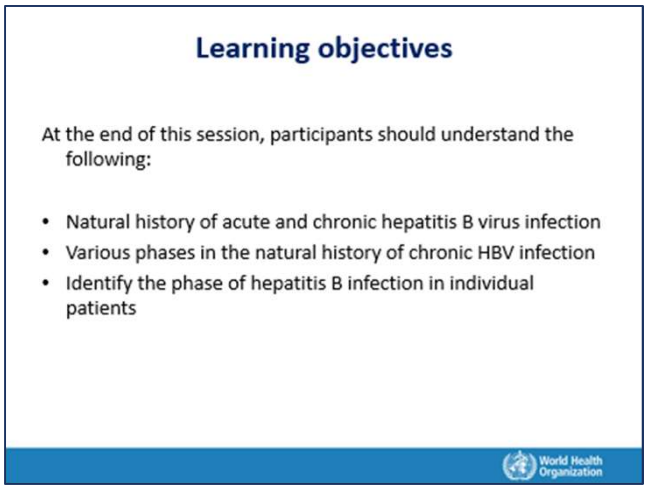
- **HIV-positive individuals** should be vaccinated as early as possible during the course of the HIV infection.
- **In immunocompromised individuals**, including patients with chronic renal failure, chronic liver disease, coeliac disease, and diabetes, the immune response following vaccination is often reduced.
- Hepatitis B vaccine can be administered safely to **pregnant and lactating women**.


Summary
• Recombinant hepatitis B vaccines are highly safe, easy to administer and effective.
• Recommended three-dose schedule provides good protection in 95% of recipients.
• Anti-HBs titre ≥10 mIU/mL indicates adequate protection.
• Birth dose provides additional protection against mother-to-child transmission (MTCT) of hepatitis B.
• Birth dose followed by two additional doses has 90% efficacy in preventing MTCT of hepatitis B.
• Booster doses of hepatitis B vaccine are not needed in the general population.
World Health Organization

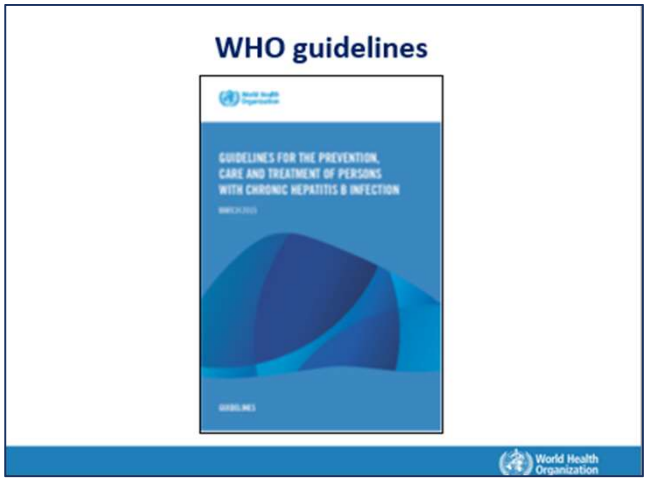
Module 7

Natural history of hepatitis B virus infection

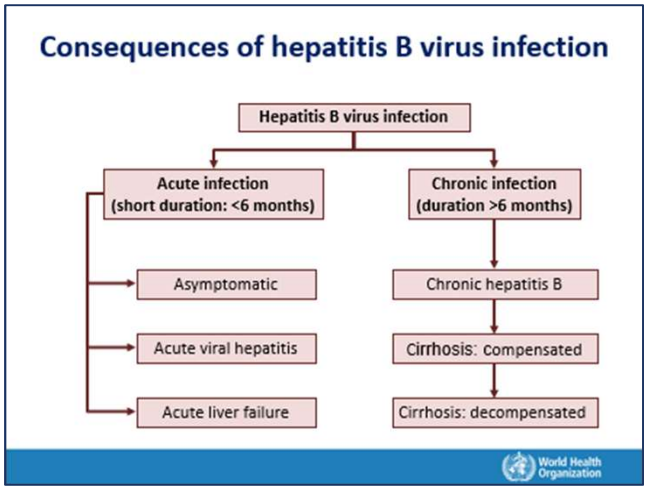
Module 7



At the end of this session, participants should understand the following:
- Natural history of acute and chronic hepatitis B virus infection
- Various phases in the natural history of chronic HBV infection
- Identify the phase of hepatitis B infection in individual patients



This module is based on the WHO HBV guidelines 2015.



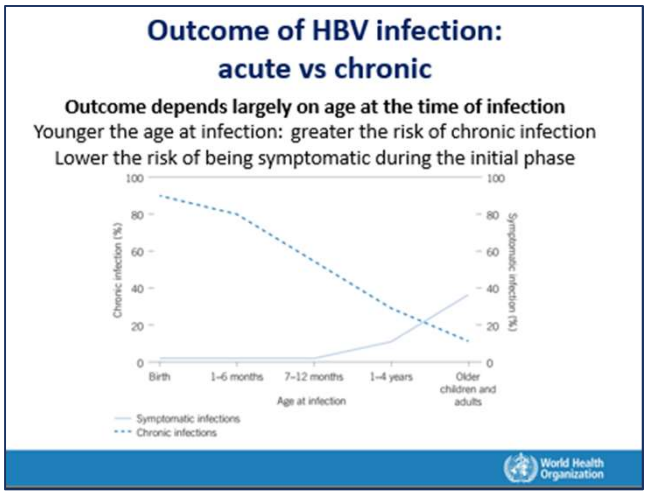
Once HBV infection is established in a host, the clinical illness may take one of the two possible courses:

First, acute infection, and second, chronic infection. The probability of developing acute or chronic infection is primarily determined by the age of the host at the time of infection (already discussed).

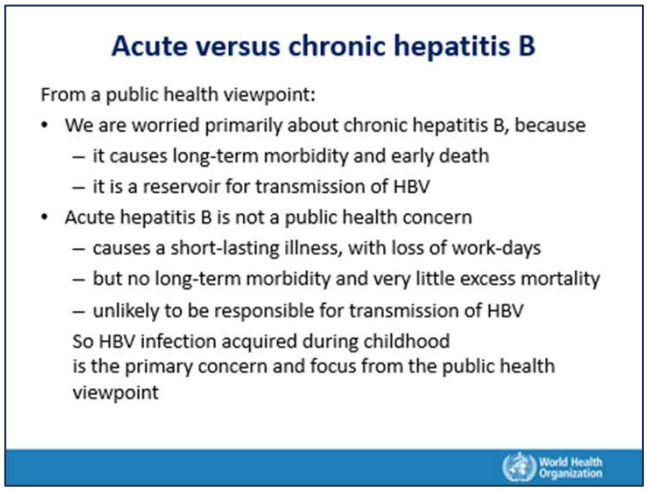
Acute infection is characterized by marked elevation of serum levels of liver enzymes; these patients clear the virus in 6 months' time.

Chronic infection remains asymptomatic and patients fail to clear the virus.
A person with acute HBV infection may remain asymptomatic, or develop features of acute viral hepatitis or progress to acute liver failure.

In a person with chronic HBV infection, the liver is constantly exposed to virus-induced injury. After decades of virus-induced liver injury followed by natural healing with fibrosis, the condition may progress to liver cirrhosis. If cirrhosis is left unchecked for a long time, patients may develop complications of cirrhosis such as ascites, variceal bleed and hepatic encephalopathy (called decompensation).



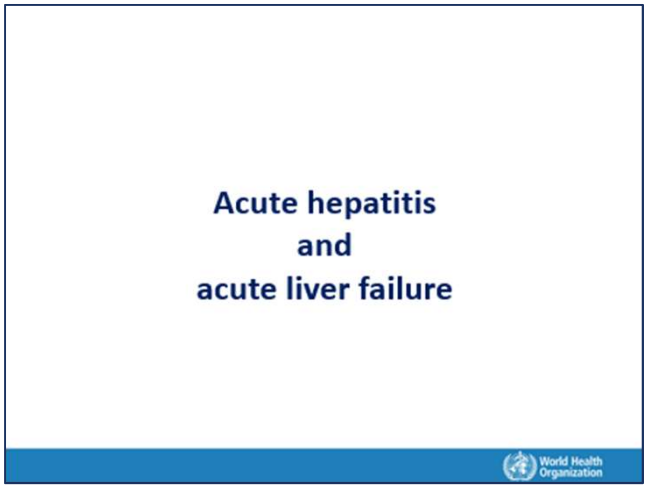
The natural history of HBV infection depends on the age of the host at the time of infection. There is an inverse relationship between the risk of developing acute hepatitis and its progression to chronic infection and the age of the host. Infections during infancy remain asymptomatic and carry more than 90% chance of progressing to chronic infection. Up till the age of 5 years, about 20% develop chronic infection. After the age of 5 years and particularly in adults, more than 90% develop acute hepatitis and clear the virus in 6 months' time.



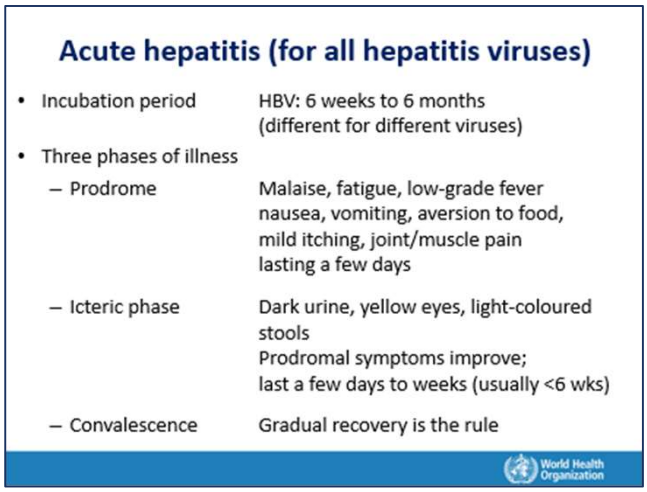
From a public health perspective, chronic hepatitis B is more important than acute hepatitis B because of several reasons:

- It causes long-term morbidity and early death.
- It acts as a reservoir for HBV transmission to a susceptible host .

In contrast, acute hepatitis B causes a short-lasting illness and poses limited medical disability, mortality and financial burden.
Further, acute hepatitis B is unlikely to be responsible for transmission of HBV. But ongoing cases of acute hepatitis B among adults indicates that measures to prevent the spread of HBV are inadequate and more efforts for prevention are needed.



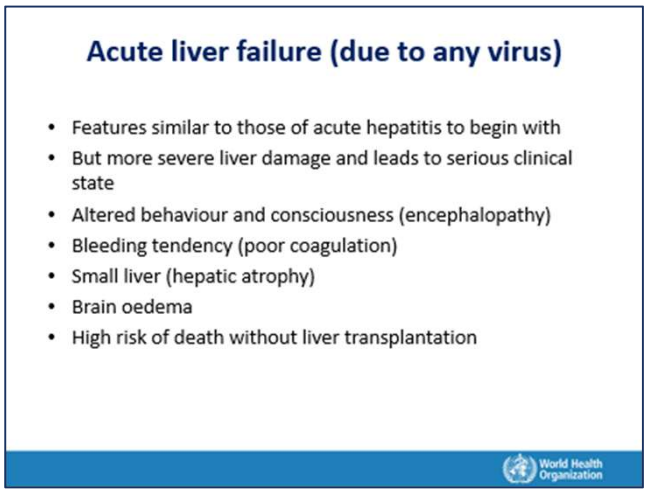
A small proportion of those with acute hepatitis may progress to develop acute liver failure. Hence, we need to know the difference between the two conditions.



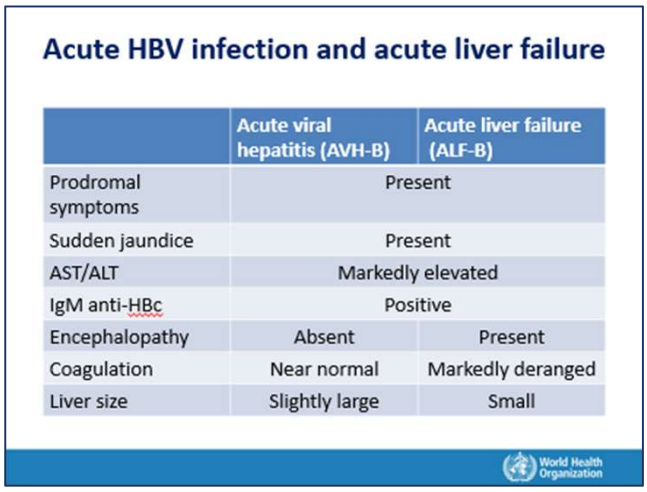
Following exposure to HBV, a susceptible host develops acute hepatitis after an incubation period of 6 weeks to 6 months.

The entire illness of acute hepatitis B sequentially passes through three phases, namely prodromal phase, icteric phase and convalescence phase. The prodromal phase is characterized by MARKED LOSS OF APPETITE, and other flu-like symptoms such as low-grade fever, nausea and vomiting, and lasts for a few days.

Once the prodromal symptoms start subsiding, the patient develop yellow discoloration of the eyes and urine (icteric phase). This phase usually lasts for a few weeks, usually less than 6 weeks. During this phase, serum levels of liver enzymes are extremely high, usually more than 20–30 times the upper limit of normal. In a period of 1–2 weeks, the icteric phase reaches its peak, which is soon followed by recovery of all the symptoms and regaining of natural well-being. Almost complete recovery is the rule.



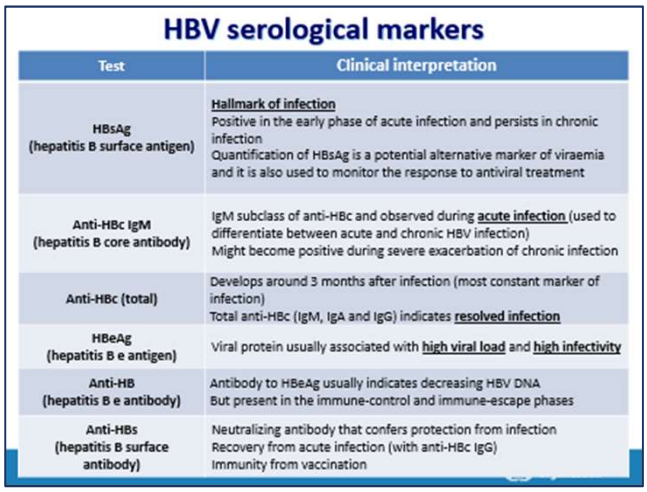
A very small proportion of those with acute hepatitis B may worsen and progress to acute liver failure, which is a life-threatening condition. The illness in a patient with acute liver failure starts with features similar to those of acute hepatitis though these patients very rapidly progress to liver failure, which is characterized by altered behaviour and altered consciousness (hepatic encephalopathy), bleeding tendency such as ecchymosis, and features of raised intracranial hypertension. Acute liver failure is a life-threatening condition. It needs to be managed in an intensive care unit, and carries about a 50% risk of death without liver transplantation.



	Acute viral hepatitis (AVH-B)	Acute liver failure (ALF-B)
Prodromal symptoms	Present	
Sudden jaundice	Present	
AST/ALT	Markedly elevated	
IgM anti-HBc	Positive	
Encephalopathy	Absent	Present
Coagulation	Near normal	Markedly deranged
Liver size	Slightly large	Small

This table summarizes the distinguishing features between acute hepatitis and acute liver failure.

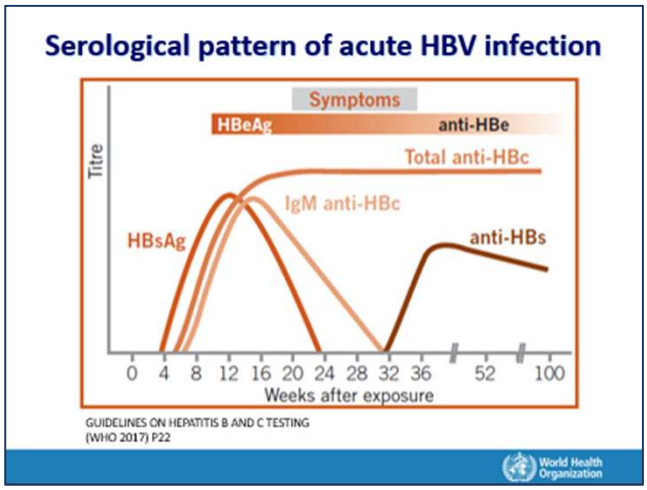
The prodromal symptoms are the same in both – jaundice, elevation of AST/ALT, and positive IgM anti-HBc, acute phase reactive immunoglobulin. The differences are the presence of encephalopathy, marked derangement in coagulation and small size of the liver in acute liver failure.



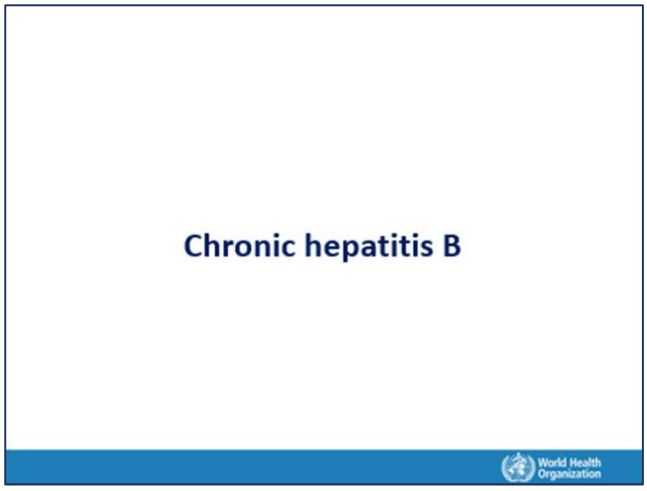
HBV serological markers

Test	Clinical interpretation
HBsAg (hepatitis B surface antigen)	Hallmark of infection Positive in the early phase of acute infection and persists in chronic infection Quantification of HBsAg is a potential alternative marker of viraemia and it is also used to monitor the response to antiviral treatment
Anti-HBc IgM (hepatitis B core antibody)	IgM subclass of anti-HBc and observed during acute infection (used to differentiate between acute and chronic HBV infection) Might become positive during severe exacerbation of chronic infection
Anti-HBc (total)	Develops around 3 months after infection (most constant marker of infection) Total anti-HBc (IgM, IgA and IgG) indicates resolved infection
HBeAg (hepatitis B e antigen)	Viral protein usually associated with high viral load and high infectivity
Anti-HB (hepatitis B e antibody)	Antibody to HBeAg usually indicates decreasing HBV DNA But present in the immune-control and immune-escape phases
Anti-HBs (hepatitis B surface antibody)	Neutralizing antibody that confers protection from infection Recovery from acute infection (with anti-HBc IgG) Immunity from vaccination

Here we introduce the various serological markers of HBV infection, which will help us to understand the various phases of acute and chronic hepatitis B. HBsAg (hepatitis B surface antigen) is the hallmark of HBV infection. Anti-HBc IgM (hepatitis B core antibody) is observed during acute infection. Anti-HBc (total antibody against HBV core antigen) indicates the presence of IgM and/or IgG against the core antigen. A positive total anti-HBc with negative anti-HBc IgM antibodies indicates resolved infection. HBeAg (hepatitis B envelope antigen) is viral protein associated usually with a high viral load and high infectivity. Anti-HBe (antibody to HBeAg) usually indicates decreasing HBV DNA. Anti-HBs is a neutralizing antibody.



This slide shows the temporal pattern of various serological markers seen in acute HBV infection. First, HBsAg appears 2–10 weeks after infection. In the next 1—2 weeks, total anti-HBc and IgM anti-HBc increase and total anti-HBc continues to be positive. HBsAg and IgM anti-HBc disappear within 6 months and anti-HBs appears. In most individuals, anti-HBs persists for life and provides long-term immunity

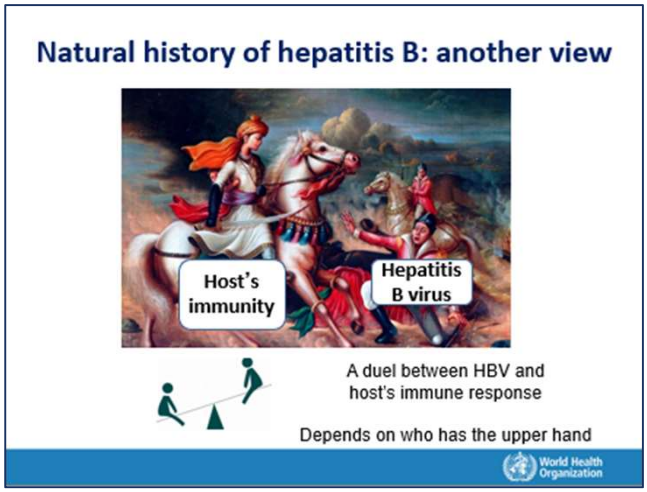


Hepatitis B can cause hepatocellular carcinoma (HCC) even without developing cirrhosis as it is a DNA virus and is integrated into the human genome. It can cause HCC due to replication and mutant types.

HCV is an RNA virus and lies in the cytoplasm only and can be eradicated as it is not integrated into the genome of the host.

Next, we will move to chronic hepatitis.

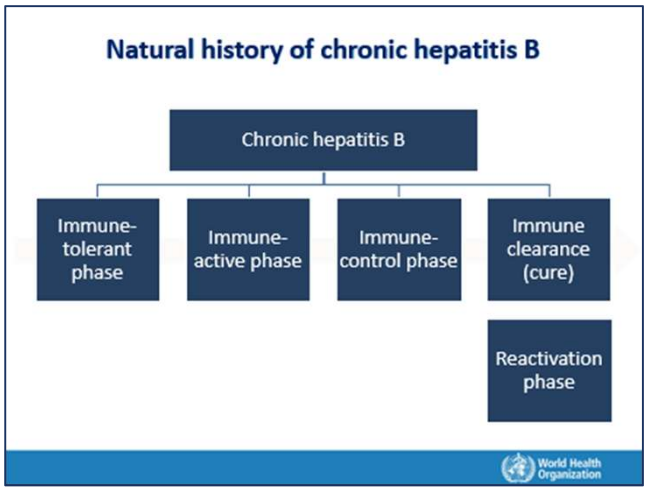
Module 7



Hepatitis B virus is not a cytotoxic virus, which means that the virus itself does not cause any injury or harm to the hepatocyte. The injury to the infected person is primarily mediated by the host's immune system. In an attempt to clear the virus, the host's immune cells and cytokines kill the hepatocyte. Hence, in an infected person, liver injury is actually a self-inflicted injury (by the immune system).

The natural history of hepatitis B is a duel between HBV and the host's immune response. If the host immune system is tolerant to the virus (immune-tolerant phase in children), there is no injury to the host despite a high viral load. In contrast, if the host immune system fights against the virus, the host will have liver injury though the viral load will be lower.

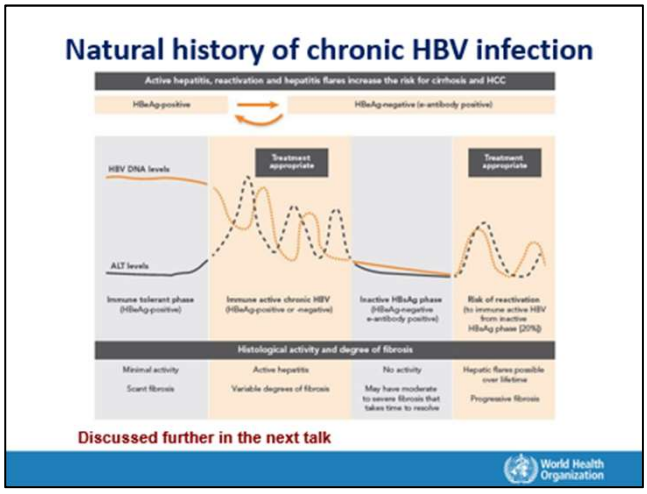
- The healing process, after cell injury, is primarily in the form of cellular regeneration and fibrosis.
- The repeated cycles of injury, healing and fibrosis ultimately result in liver cirrhosis.



The natural history of chronic hepatitis B infection can be divided into 4 phases: immune-tolerant phase, immune-active phase, immune-control phase, and immune clearance. It is not uncommon to see a backward shift in phase and reactivation of disease from the immune clearance phase.

The sequence of all these four phases is typically seen in children are infected through perinatal transmission and are followed at regular intervals from birth.

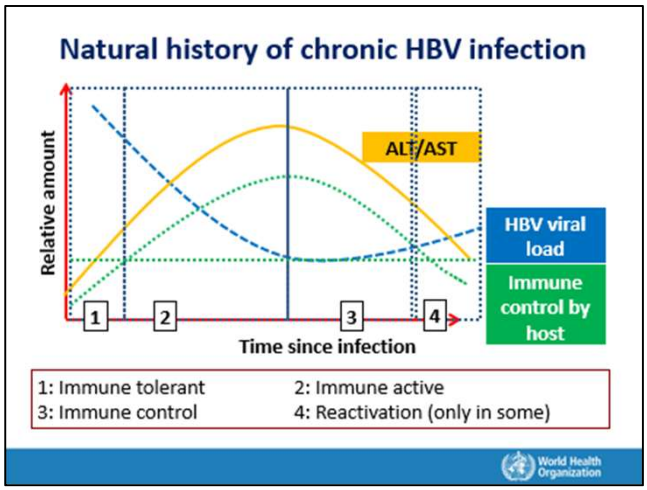
Among adults, on first detection of HBV infection, the infected person might be in any one of the four phases. The priority task will be to evaluate and follow the person for 6–12 months to determine which phase the person is in.



The natural history of chronic HBV infection is complex. It comprises the immune-tolerant phase, immune-active chronic phase, inactive HBsAg phase and reactivation.

The four phases differ from each other in certain parameters such as serum ALT level, HBeAg status and viral load.

This is discussed in the next talk.

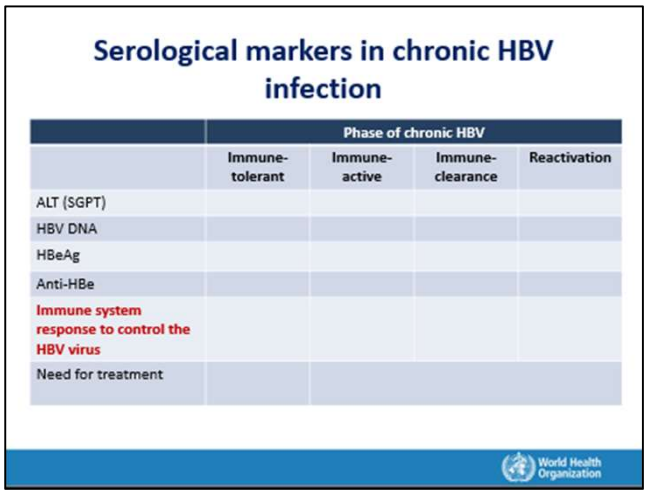


This slide shows the concept of the natural history of chronic HBV infection. The blue line shows the viral load. Yellow line is the levels of AST/ALT during hepatitis. Green indicates the host immune response. In the immune-tolerant phase, the host immunity against HBV is weak. So, the viral load is high. AST/ALT is low because there is no attack on the infected hepatocytes by the weak host immune system.

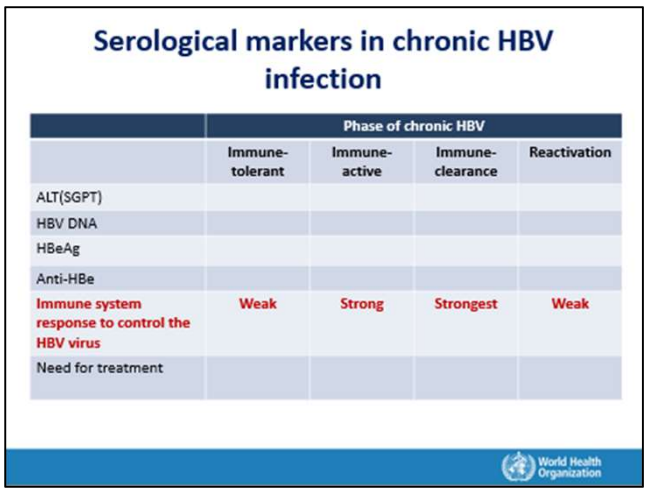
In the immune-active phase, host immunity become strong and infected hepatocytes are attacked, and AST/ALT increases. Thus, viral load decreases.

In the immune-control phase, host immunity becomes stronger and can control the viral load.

In the reactivation phase, in case of a weakened host immunity caused by drugs such as immunosuppressive agents, the viral load increases.



We will summarize the serological markers in chronic HBV infection. Immune-tolerant, immune-active, immune-clearance and reactivation phases.



First, let's think of the body's immune system response to control the hepatitis B virus.

In the immune-tolerant phase, immunity is weak; in the immune-active phase it is strong; in the immune-clearance phase strongest, and in the reactivation phase it is weak.

Serological markers in chronic HBV

	Phase of chronic HBV			
	Immune-tolerant	Immune-active	Immune-clearance	Reactivation
ALT(SGPT)	Low			
HBV DNA	High			
HBeAg	+			
Anti-HBe	-			
Immune system response to control the HBV virus	**Weak**	**Strong**	**Strongest**	**Weak**
Need for treatment	**No**			

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In the immune-tolerant phase, because of weak host immune response, ALT is low. HBV DNA is high. HBeAg is positive and anti-HBe is negative, reflecting a high viral load. This phase does not need treatment.

Treatment is not needed as we do not need to clear the virus – however, it is important to check for liver injury. If there is no liver injury (evidenced by liver function tests), no treatment is required.

Other points weighing the balance and risks of starting antiviral drugs for treatment early, is that, if there is treatment interruption and development of drug resistance, the antiviral drug may not be available for the individual in the future.

Serological markers in chronic HBV

	Phase of chronic HBV			
	Immune-tolerant	Immune-active	Immune-clearance	Reactivation
ALT (SGPT)	Low	High		
HBV DNA	High	Moderate		
HBeAg	+	+/-		
Anti-HBe	-	-/+		
Immune system response to control the HBV virus	**Weak**	**Strong**	**Strongest**	**Weak**
Need for treatment	**No**	**Yes**		

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In the immune-active phase, host immunity is strong, ALT is high and HBV DNA viral load is moderate. HBeAg and anti-HBe are positive or negative. In this phase, antiviral treatment is needed because liver injury is ongoing. In this phase as well, the individual can progress directly to developing hepatocellular carcinoma (HCC).

Serological markers in chronic HBV

	Phase of chronic HBV			
	Immune-tolerant	Immune-active	Immune-clearance	Reactivation
ALT (SGPT)	Low	High	Moderate	
HBV DNA	High	Moderate	Low	
HBeAg	+	+/-	-/+	
Anti-HBe	-	-/+	+/-	
Immune system response to control the HBV virus	**Weak**	**Strong**	**Strongest**	**Weak**
Need for treatment	**No**	**Yes**	**No**	

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In the immune-clearance phase, host immune response is the strongest. ALT is moderately increased. HBV DNA is controlled and low. Treatment is not needed during this phase.

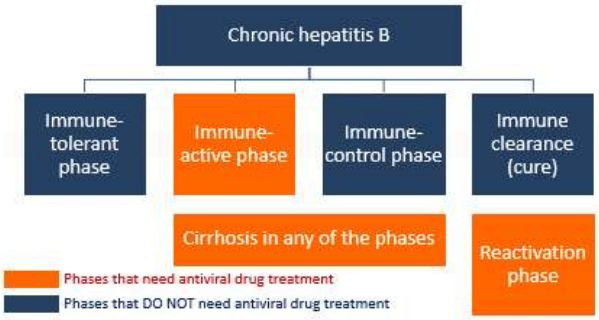
Serological markers in chronic HBV

	Immune phase of chronic HBV			
	Immune-tolerant	Immune-active	Immune-clearance	Reactivation
ALT/SGPT	Low	High	Moderate	Low/mod
HBV DNA	High	Moderate	Low	Low/mod
HBeAg	+	+/-	-/+	-/+
Anti-HBe	-	-/+	+/-	+/-
Anti-HBV immune control	**Weak**	**Strong**	**Strongest**	**Weak**
Need for treatment	No	Yes	No	Yes

World Health Organization

Reactivation is a specific phase. The markers are varied. Antiviral treatment is required during this phase.

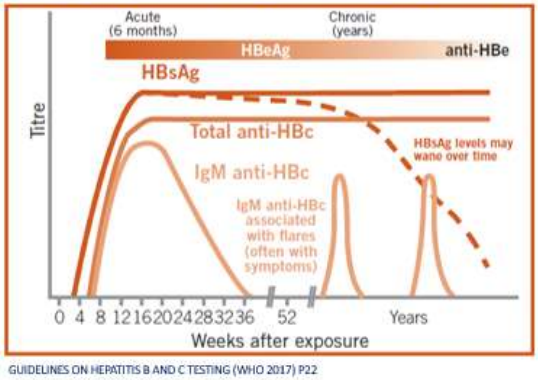
Natural history of chronic hepatitis B



World Health Organization

Individuals assessed to be in the ORANGE phases of chronic hepatitis B infection need initiation of treatment.
These are:
- immune-active phase,
- cirrhosis in any of the phases, and
- the reactivation phase.

Serological pattern of chronic HBV infection



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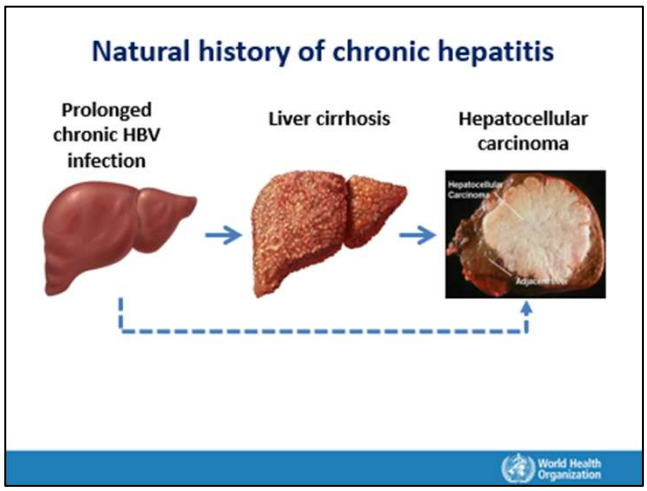
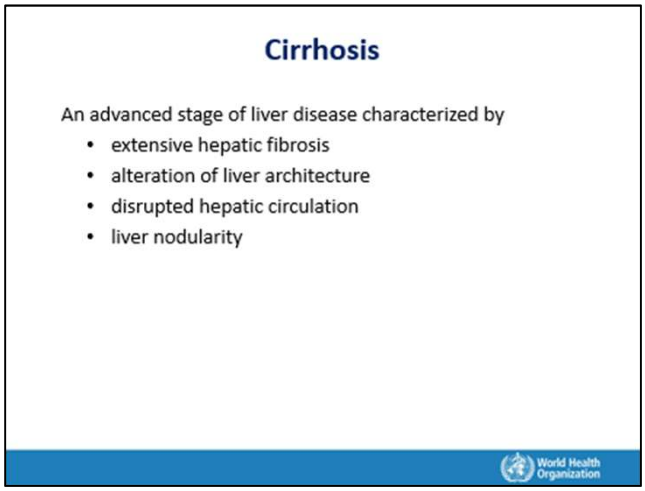
This slide shows the serological pattern of chronic HBV infection. Basically, HBsAg and anti-HBc continue to be positive and HBeAg gradually decreases and anti-HBe becomes positive, which is a minor seroconversion. In some cases, IgM anti-HBc becomes positive at a low level and is associated with a hepatitis flare. HBsAg levels may wane over time in older age groups.



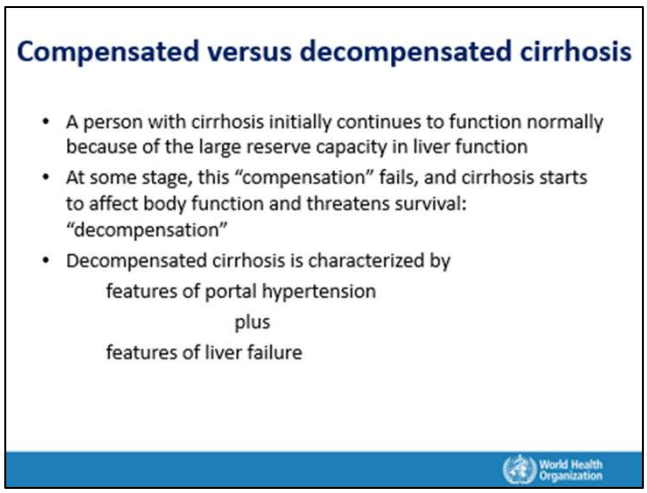
This slide shows the natural history of chronic hepatitis. Prolonged HBV chronic infection may result in cirrhosis and hepatocellular carcinoma (liver cancer).

In the case of HBV chronic infection, hepatocellular carcinoma can develop at any time, even in the absence of cirrhosis (i.e. the liver is not cirrhotic) This is one reason why, regular ultrasound scan screening for liver masses among people living with chronic infection is recommended.



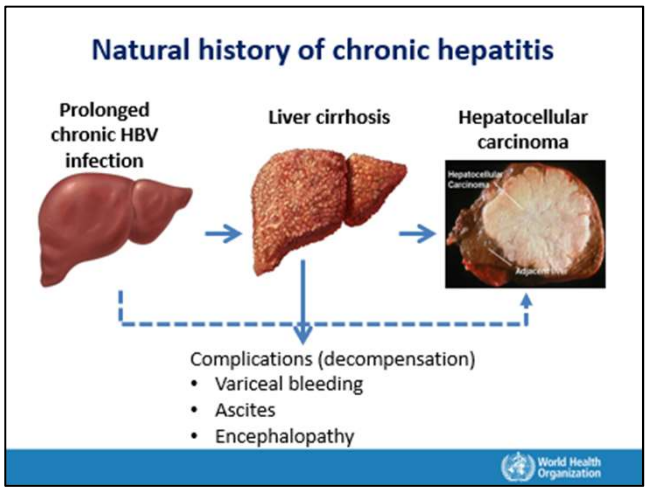
Cirrhosis is defined as,

- extensive hepatic fibrosis
- alteration of liver architecture
- disrupted hepatic circulation
- liver nodularity

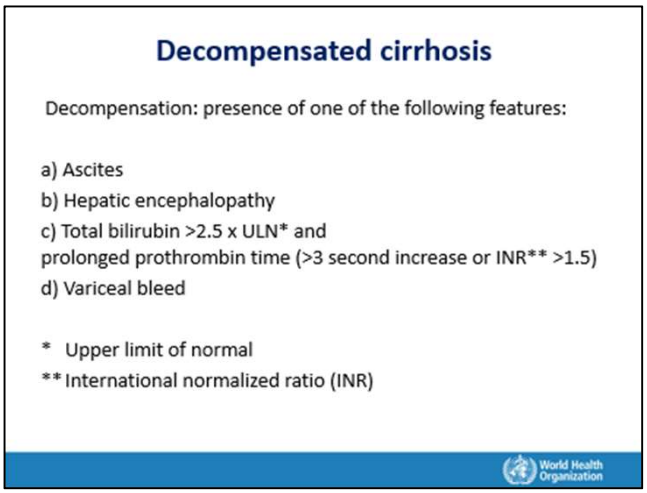


There are 2 clinical states of cirrhosis: compensated and decompensated. A person with cirrhosis initially continues to function normally because of the large reserve capacity in liver function. At some stage, this "compensation" fails, and cirrhosis starts to affect body function and threatens survival: "decompensation". Decompensated cirrhosis is characterized by

features of portal hypertension
plus
features of liver failure.

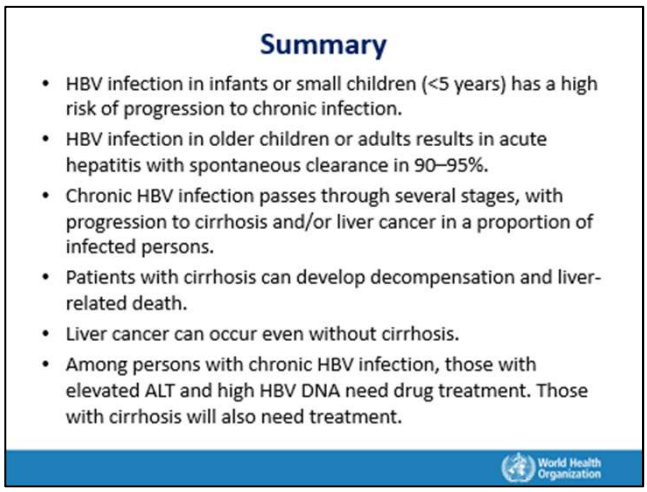


So, cirrhosis with complications such as variceal bleeding, ascites and encephalopathy is defined as "decompensated".



Decompensation is defined by the presence of one of the following features:

a) Ascites
b) Hepatic encephalopathy
c) Total bilirubin >2.5 x ULN* + prolonged prothrombin time (>3 second increase or INR** >1.5)
d) Variceal bleed



In summary,
HBV infection in infants or small children (<5 years) has a high risk of progression to chronic infection. HBV infection in older children or adults results in acute hepatitis with spontaneous clearance in 90–95%.

Chronic HBV infection passes through several stages, with progression to cirrhosis and/or liver cancer in a proportion of infected persons. Patients with cirrhosis can develop decompensation and liver-related death.

Liver cancer can occur even without cirrhosis. Among persons with chronic HBV infection, only those with elevated ALT and high HBV DNA need drug treatment. Those with cirrhosis will also need treatment.

Module 8

Testing and serological markers for hepatitis B virus

Learning objectives

At the end of this session, the participants should:

- Know about various serological markers of HBV infection
- Understand the use of HBV markers in differentiating between various phases of HBV infection
- Understand the testing approach in HBV

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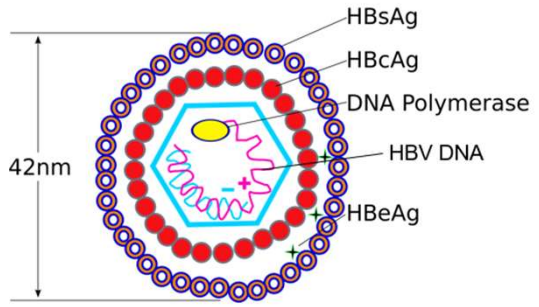
At the end of this session, participants should:
- Know about various serological markers of HBV infection
- Understand the use of HBV markers in differentiating between various phases of HBV infection
- Understand the testing approach in HBV

Structure of HBV viral particle



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This slide shows the structure of the HBV viral particle:
- HBsAg, HBV surface antigen is on surface of virus.
- There is nucleocapsid, core, in inside of viral particle.
- HBcAg, HBV core antigen is on surface of nucleocapsid.
- HBV DNA is inside of nucleocapside.
- HBeAg, HBV envelope antigen, is located between HBV surface and core.

Types of serological markers

Antigen-antibody		Nucleic acid
Antigen	Antibody	
HBsAg (Hepatitis B surface Antigen)	Anti-HBs (HB surface antibody)	HBV DNA (qualitative or quantitative)
HBcAg (Hepatitis B core Antigen) Does not appears in blood	IgM anti-HBc (HB core antibody IgM)	
	Total anti-HBc (IgM plus IgG)	
HBeAg (Hepatitis B e Antigen)	Anti-HBe (Hepatitis B e antibody)	

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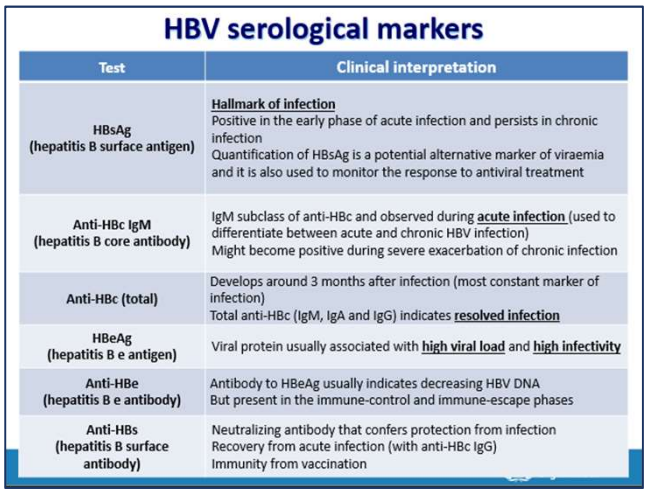
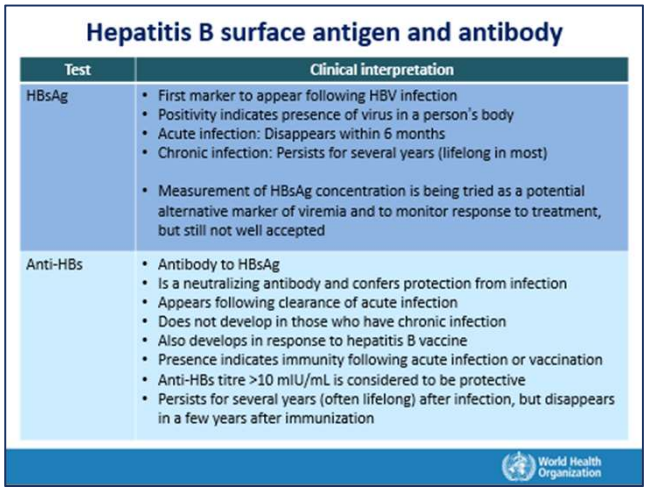
This table shows types of serological markers:
- HBsAg means Hepatitis B surface antigen, Anti-HBs means HB surface antibody
- HBcAg means Hepatitis B core antigen, IgM anti-HBc means HB core antibody IgM
- Total anti-HBc means IgM and IgG
- HBeAg means Hepatitis B envelope antigen, Anti-HBe means Hepatitis B envelope antibody.



HBV serological markers

Test	Clinical interpretation
HBsAg (hepatitis B surface antigen)	**Hallmark of infection** Positive in the early phase of acute infection and persists in chronic infection Quantification of HBsAg is a potential alternative marker of viraemia and it is also used to monitor the response to antiviral treatment
Anti-HBc IgM (hepatitis B core antibody)	IgM subclass of anti-HBc and observed during **acute infection** (used to differentiate between acute and chronic HBV infection) Might become positive during severe exacerbation of chronic infection
Anti-HBc (total)	Develops around 3 months after infection (most constant marker of infection) Total anti-HBc (IgM, IgA and IgG) indicates **resolved infection**
HBeAg (hepatitis B e antigen)	Viral protein usually associated with **high viral load** and **high infectivity**
Anti-HBe (hepatitis B e antibody)	Antibody to HBeAg usually indicates decreasing HBV DNA But present in the immune-control and immune-escape phases
Anti-HBs (hepatitis B surface antibody)	Neutralizing antibody that confers protection from infection Recovery from acute infection (with anti-HBc IgG) Immunity from vaccination

Here, we introduce the various serological markers of HBV infection, which will help us to understand the various phases of acute and chronic hepatitis B. HBsAg (hepatitis B surface antigen) is the hallmark of HBV infection. Anti-HBc IgM (hepatitis B core antibody) is observed during acute infection. Anti-HBc (total antibody against HBV core antigen) indicates the presence of IgM and/or IgG against the core antigen. A positive total anti-HBc with negative anti-HBc IgM antibodies indicates resolved infection. HBeAg (hepatitis B envelope antigen) is viral protein associated usually with a high viral load and high infectivity. Anti-HBe (antibody to HBeAg) usually indicates decreasing HBV DNA. Anti-HBs is a neutralizing antibody.



Hepatitis B surface antigen and antibody

Test	Clinical interpretation
HBsAg	• First marker to appear following HBV infection • Positivity indicates presence of virus in a person's body • Acute infection: Disappears within 6 months • Chronic infection: Persists for several years (lifelong in most) • Measurement of HBsAg concentration is being tried as a potential alternative marker of viremia and to monitor response to treatment, but still not well accepted
Anti-HBs	• Antibody to HBsAg • Is a neutralizing antibody and confers protection from infection • Appears following clearance of acute infection • Does not develop in those who have chronic infection • Also develops in response to hepatitis B vaccine • Presence indicates immunity following acute infection or vaccination • Anti-HBs titre >10 mIU/mL is considered to be protective • Persists for several years (often lifelong) after infection, but disappears in a few years after immunization

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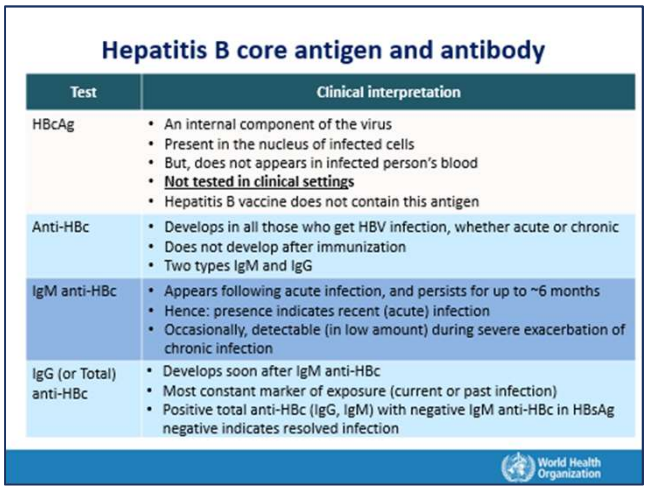

Hepatitis B core antigen and antibody

Test	Clinical interpretation
HBcAg	• An internal component of the virus • Present in the nucleus of infected cells • But, does not appears in infected person's blood • **Not tested in clinical settings** • Hepatitis B vaccine does not contain this antigen
Anti-HBc	• Develops in all those who get HBV infection, whether acute or chronic • Does not develop after immunization • Two types IgM and IgG
IgM anti-HBc	• Appears following acute infection, and persists for up to ~6 months • Hence: presence indicates recent (acute) infection • Occasionally, detectable (in low amount) during severe exacerbation of chronic infection
IgG (or Total) anti-HBc	• Develops soon after IgM anti-HBc • Most constant marker of exposure (current or past infection) • Positive total anti-HBc (IgG, IgM) with negative IgM anti-HBc in HBsAg negative indicates resolved infection

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Hepatitis B e-antigen and antibody

Test	Clinical interpretation
HBeAg	• Produced in cells where virus is actively replicating, and is secreted into the plasma • Usually its presence indicates high viral load and high infectivity • Its absence indicates lower viral load, lower HBV DNA level. But, in some, may be absent despite high viral load (due to viral mutation) • Associated with high risk of HBV transmission following exposure, such as needle-stick injury, mother-to-child transmission, etc.
Anti-HBe	• Indicates host immune response against HBeAg • Usually associated with reduced viral replication, lower HBV DNA titer and reduced infectivity • But also present in those in HBeAg-negative viral mutation
HBV DNA	• Direct and accurate marker of HBV replication • Serum level seems to correlate with the risk of disease progression • Used to decide need for anti-viral drugs • Also used to monitor efficacy of anti-viral drug treatment • Unit: almost 5 copies = 1 IU

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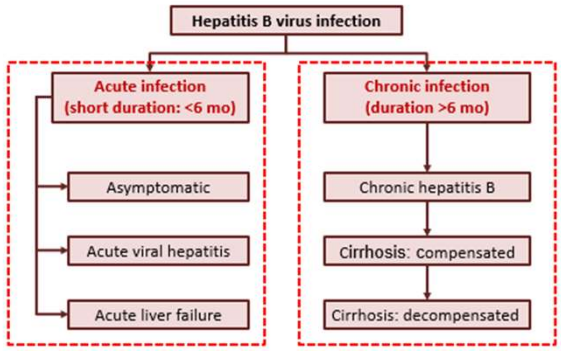
Consequences of hepatitis B virus infection



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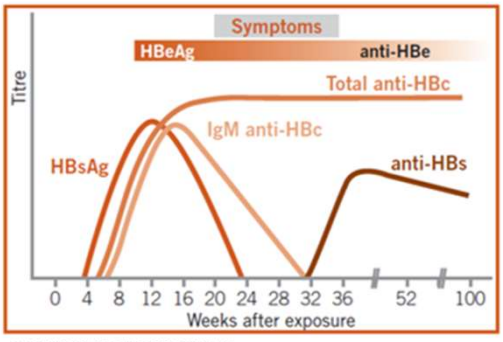
The consequences of hepatitis B virus infection are divided into two clinical courses:
- After hepatitis B virus infection, the individual may have acute infection, which is defined as infection duration less than 6 months, OR chronic infection, where the infection duration lasts more than 6 months.

- In acute infection, the patient may be/have:
(a) Asymptomatic: the infected persons have no clinical symptoms and they do not notice the infection.
(b) Acute viral hepatitis: the infected persons have clinical symptoms such as general malaise, appetite loss or flu-like symptoms and usually they resolve with no treatment or only needing supportive care.
(c) In acute liver failure: the infected persons have severe clinical symptoms related to liver failure, such as jaundice, ascites and hepatic encephalopathy. In this stage, patients generally will not be able to recover without liver transplantation (i.e. mortality is high).

- In chronic infection, hepatitis B virus infection causes chronic hepatitis and the chronic inflammation over the next 20 – 30 years, after which may result in development of cirrhosis.

Serological pattern of acute HBV infection



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This figure shows the serological pattern of acute HBV infection:
- After infection, first, HBsAg appears and increase within 2-10 weeks.
- Next, IgM anti-HBc and total anti-HBc increases after 2 weeks
- IgM anti-HBc is a specific marker for acute HBV infection and it decrease and disappears after 32 weeks.
- Total anti-HBc, mainly IgG anti-HBc continues to be positive for life. Thus, total anti-HBc is the marker for post-infection.
- HBsAg decrease and disappears within 6 months, with acute infection.
- After that, the neutralizing antibody, anti-HBs, appears. In this phase, the person is considered as cured.

Interpretation of serological markers

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
-			-	Never exposed

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We will now look at interpreting the panel of HBV serological markers. This is important in clinical practice when you receive results back from the laboratory.

HBsAg negative and Anti-HBs negative means “never exposed”.

Interpretation of serological markers

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
-	+	-	+	Past natural infection, cleared, immunity achieved

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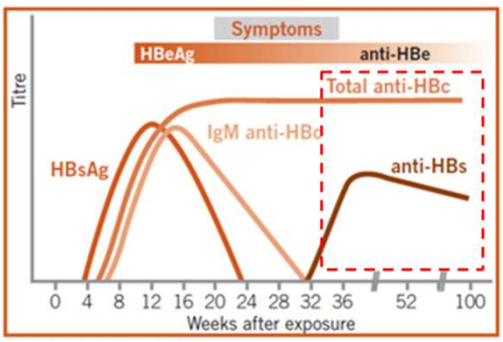
Total anti-HBC positive and anti-HBs positive means “past natural infection, cleared and immunity achieved”.

Serological pattern of acute HBV infection



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In this figure, the red dash box shows “past natural infection, cleared and immunity achieved”
- where total anti-HBC and anti-HBs tests are positive

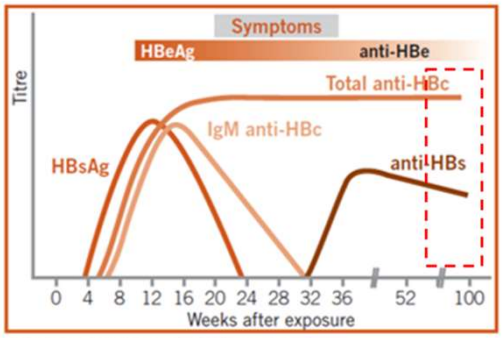
Interpretation of serological markers

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
-	+	-	-	Past natural infection, cleared, anti-HBs has waned over time

World Health Organization

Total anti-HBC only positive also means past natural infection, cleared and anti-HBs levels have waned over time.

Serological pattern of acute HBV infection



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This figure illustrates waning of the anti-HBs levels, which have dropped and disappeared over time, and where total anti-HBC remains positive.

Interpretation of the test: “past natural infection, infection cleared and anti-HBs levels have waned over time”.

Interpretation of serological markers

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
-	-	-	+	Immunity due to vaccination

World Health Organization

Anti-HBs only positive means “immunity due to vaccination”.

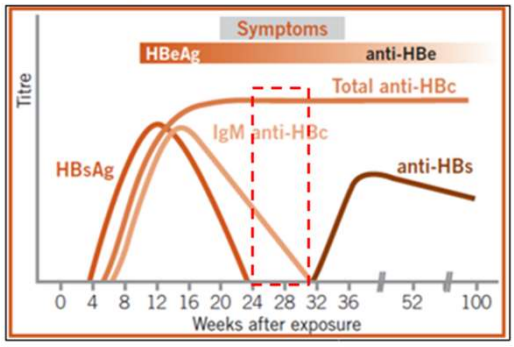
Interpretation of serological markers

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
-	+	+	+	Recent infection, recovered, immunity achieved

World Health Organization

HBs negative, total anti-HBc positive, IgM anti-HBc positive and anti-HBs positive means “recent infection, recovered, immunity achieved”.

Serological pattern of acute HBV infection



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In this figure illustrate the above slide on “recent infection, recovered, immunity achieved”.

Noted the red dash box: Anti-HBs levels have dropped and disappeared.

Interpretation of serological markers

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
+	+	+	-	Acute infection, ongoing

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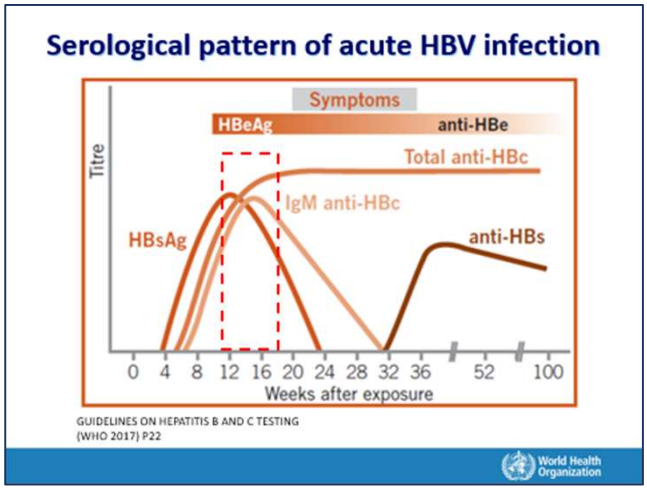
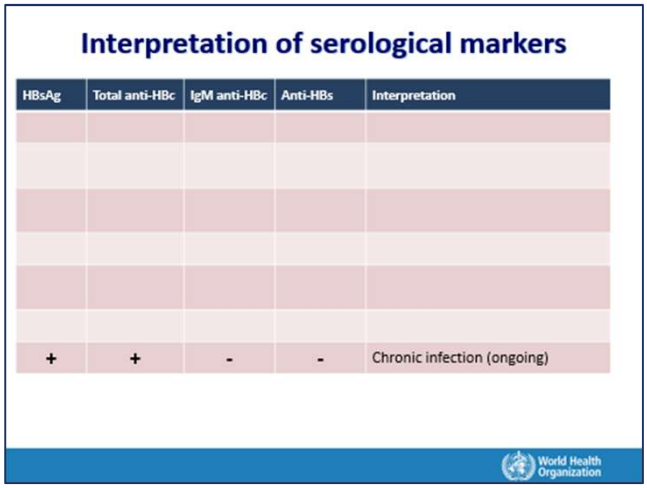
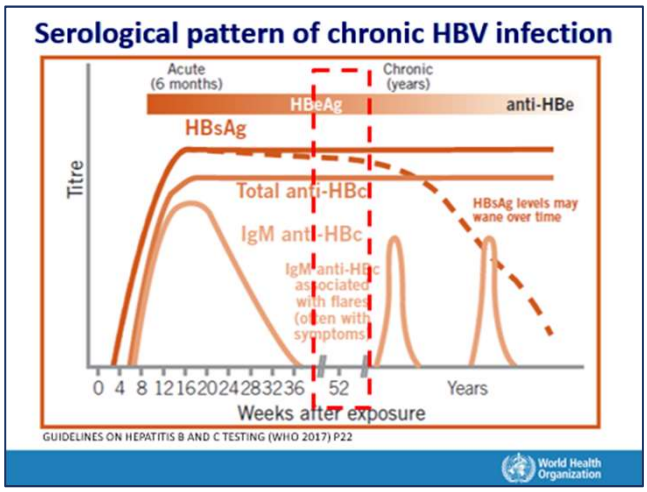
HBs positive , total anti-HBc positive, IgM anti-HBC positive and anti-HBc negative means “acute infection, ongoing”.



In this figure (red dash box) illustrates that "acute infection, is ongoing", and where HBs is positive , total anti-HBc is positive, IgM anti-HBC is positive and anti-HBc is negative

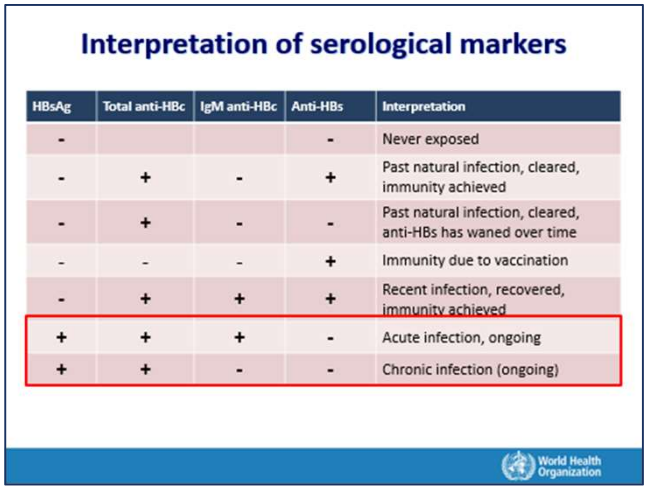


HBsAg positive, total anti-HBc positive, IgM anti-HBc negative and anti-HBs negative means chronic infection is ongoing.

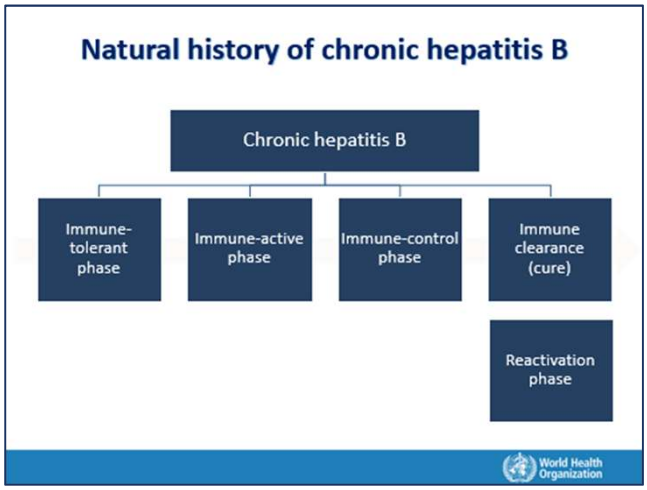


Let's have a look at the serological pattern of CHRONIC infection

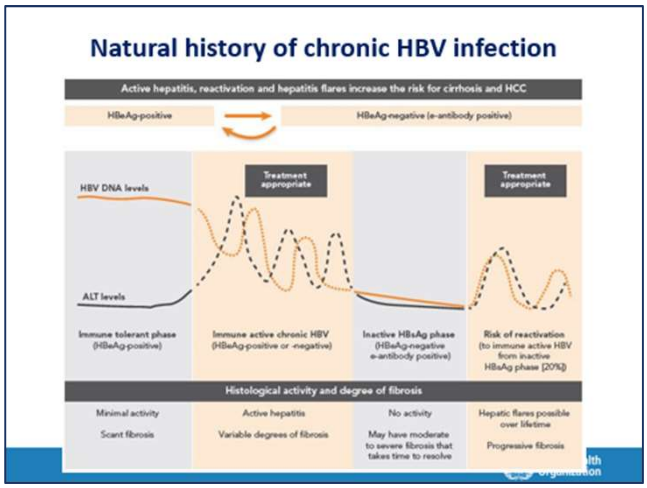
This is the part of the red dash box – where chronicity is being established, and the person moves into a chronic phase.



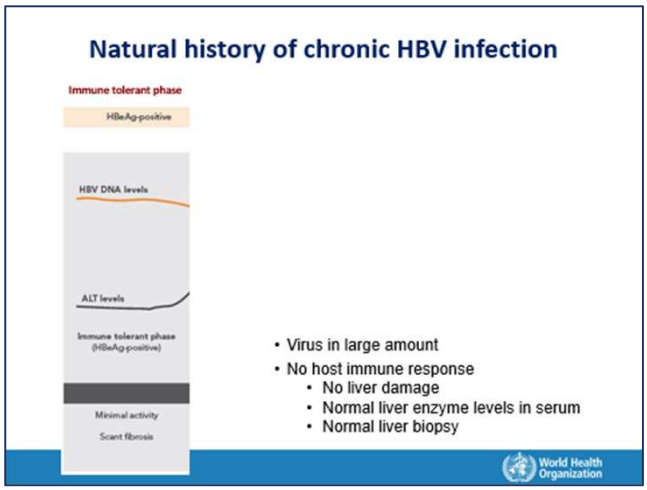
This is summary table of interpretation of serological markers. Take some time to understand this:
- From the point of screening for HBV infection, the lower two (boxed part) is important.
- If HBsAg is positive after screening, IgM anti-HBc is useful to differentiate between acute and chronic infection. However, IgM anti-HBc may not be affordable or available in resource-limiting settings.
- In such cases, clinical symptoms related to acute hepatitis or chronic infection are useful.



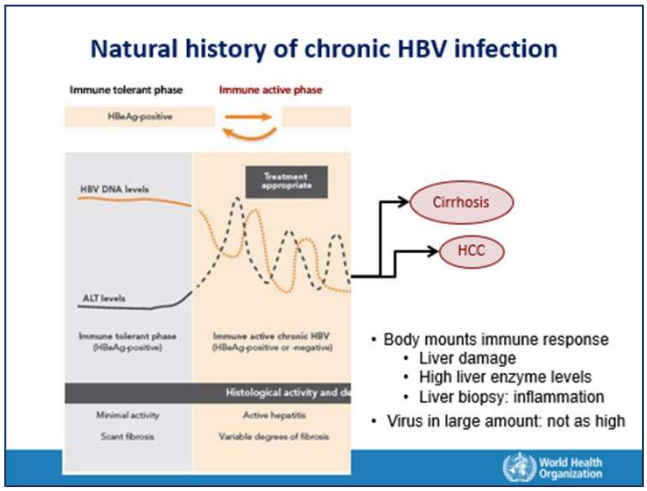
The natural history of chronic hepatitis is shown in this slide.
- There are basically 4 phases, immune-tolerant phase, immune-active phase, immune-control phase and immune clearance, cure phase.
- Another is reactivation phase, this is specific situation.



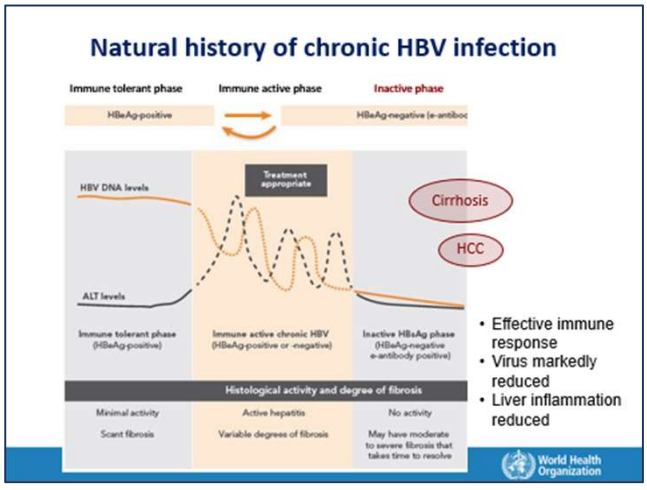
This is graph of ALT level and HBV DNA level during natural history of chronic HBV infection.



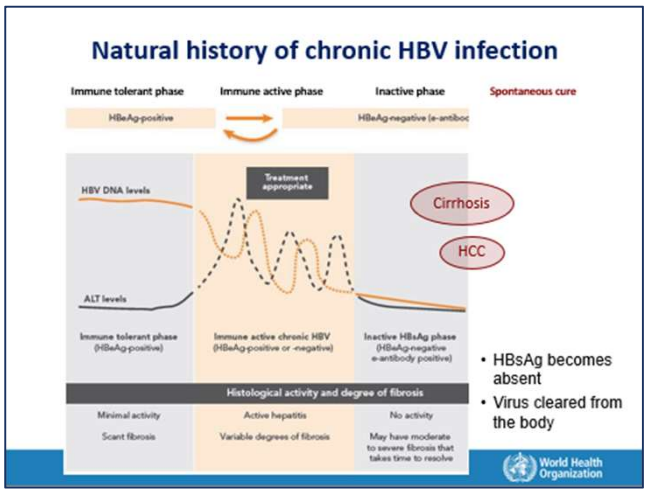
- In the immune tolerant phase, large amount of viruses in blood, but there is no host immune response.
- Therefore, there is no liver damage, and liver enzyme levels in serum is normal.
- Liver biopsy shows little inflammation.



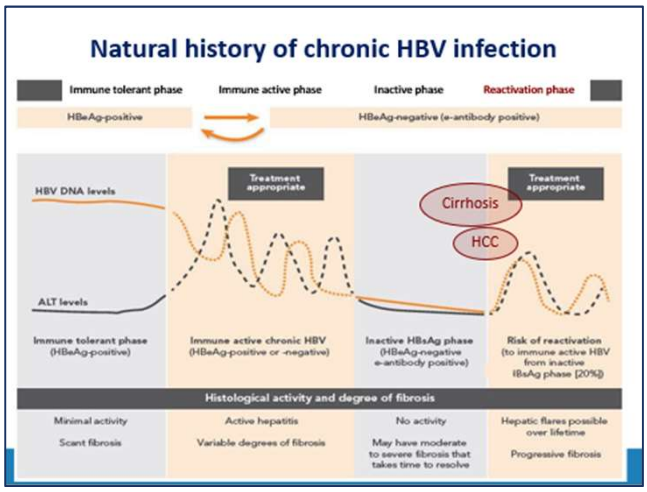
In the immune active phase, the body mounts an immune response.
- The liver is damaged by host immunity.
- Liver enzyme levels are elevated and flatulated.
- Liver biopsy shows various grades inflammation.
- But, virus levels (i.e. viral load) which is the HBV DNA, is not high compared to the immune tolerant phase and viral levels often fluctuated.
- If this phase where the viral levels remain relatively high, liver cirrhosis or HCC can develop.



In the inactive HBsAg phase, HBeAg positive becomes negative.
- The host immune response is effective in controlling the hepatitis B virus.
- ALT levels markedly decreases and viral load markedly reduced.
- Liver biopsy shows reduced inflammation.
- However, even in this phase, the risk for cirrhosis or HCC remain.

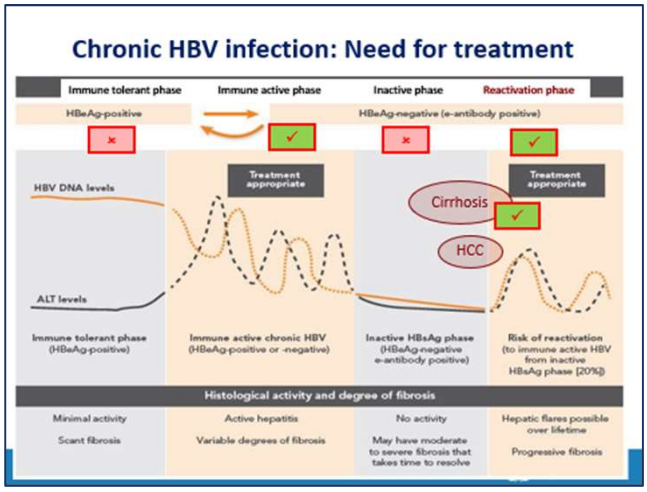


In some case, HBsAg become absent and the HBV virus is cleared from the body.
- This is immune clearance, that is, the "functional cure" phase (where HBsAg is negative, in a previously documented chronically infected individual).

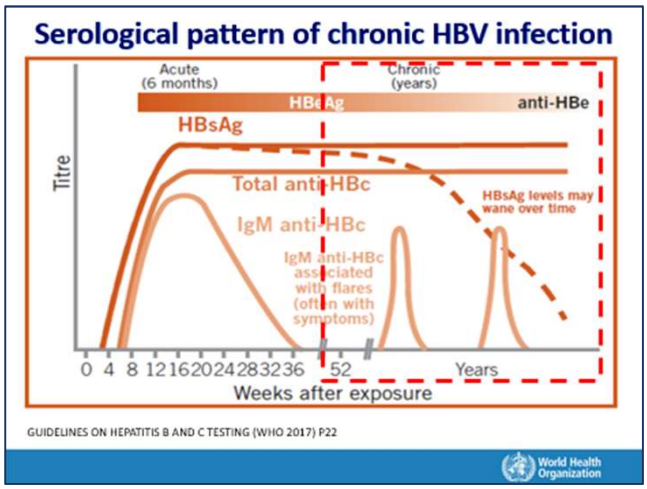


In the reactivation phase, there is a sudden increase in HBV replication (where the viral load increases) in a patient with previously immune inactive stage. Reactivation can happen spontaneously, but is typically triggered by immunosuppressive therapy of cancer, autoimmune disease, or organ transplantation.

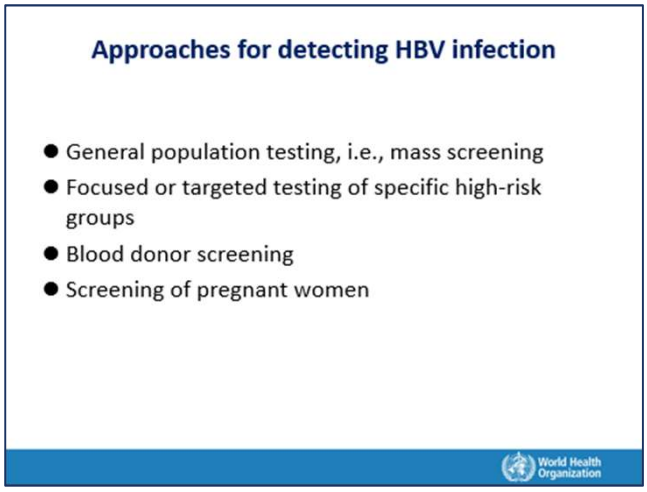
Note: among people with HBV/HCV coinfection – HBV reactivation can occur during treatment of the HCV infection, and thus may need to be provide HBV drugs during this period.



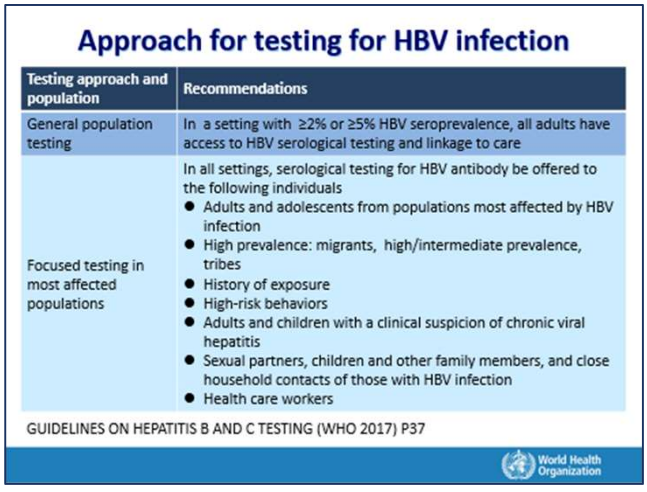
Treatment is needed for immune active phase and reactivation phase [green boxes with ticks]
Cirrhosis with any phase also need provision of treatment [green box with ticks]
On the other hand, in immune tolerant phase and inactive phase, there is no need for treatment [red boxes]



To review: this slide shows the serological pattern of chronic HBV infection.
- Basically HBsAg and anti-HBc continue to be positive.
- HBeAg gradually decreases and finally anti-HBe become positive (this is often called “minor seroconversion”)
- In some case, IgM anti-HBc become positive with low level associated with hepatitis flare.
- HBsAg levels may wane over time as age increases (especially in elderly people).



Next, let’s talk about approaches for detecting HBV infection.
There are four approaches for testing:
- General population testing, i.e., mass screening
- Focused or targeted testing of specific high-risk groups e.g. people living with HIV, prisoners, people who inject drugs, other at-risk groups, older people more than 40 years of age (testing by birth cohort), people who received unscreened/unsafe blood and blood products etc.
- Blood donor screening (usually compulsory for blood banks)
- Screening of pregnant women (as part of integrated antenatal services towards triple elimination of mother to child transmission of HIV, syphilis and viral hepatitis).



Module 8

Approach for testing for HBV infection

Testing approach and population	Recommendations
Pregnant women screening	In a setting with ≥2% or ≥5% HBV seroprevalence, routine testing of pregnant women for HBV infection is recommended
Blood donors screening	In all setting, all donors have to be screened for HBV infection

GUIDELINES ON HEPATITIS B AND C TESTING (WHO 2017) P37 World Health Organization

Country adaptation of the WHO guidelines for testing for hepatitis B and C is needed.
Testing for target groups and people at risk should be determined

How to test for chronic HBV infection

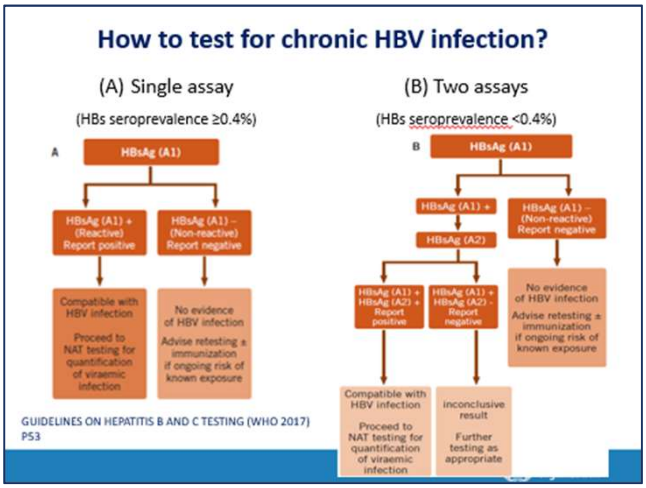
Topic	Recommendations
Which serological assays to use	For the diagnosis of chronic HBV infection, a serological assay (in **either RDT or laboratory-based immunoassay format**) is recommended to detect **hepatitis B surface antigen (HBsAg).** - In settings where existing laboratory testing is already available and accessible, laboratory-based immunoassays are recommended as the preferred assay format. - In settings where there is limited access to laboratory testing and/or in populations where access to rapid testing would facilitate linkage to care and treatment, use of RDTs is recommended.
Serological testing strategies	• In settings or populations with an **HBsAg seroprevalence of ≥0.4%, a single serological assay** for detection of HBsAg is recommended, prior to further evaluation for HBV DNA and staging of liver disease. • In settings or populations with a **low HBsAg seroprevalence of <0.4%**, confirmation of HBsAg positivity on the same immunoassay with a neutralization step or a second different RDT assay for detection of HBsAg may be considered.

GUIDELINES ON HEPATITIS B AND C TESTING (WHO 2017) P52 World Health Organization

For the diagnosis of chronic HBV infection, a serological assay (in either RDT or laboratory-based immunoassay format) is recommended to detect hepatitis B surface antigen (HBsAg).

WHO outlines two strategies for HBV serological testing in setting with HBsAg seroprevalence.
- In high HBsAg seroprevalence of more than 0.4%, single serological assay.
- In low HBsAg seroprevalence of less than 0.4%, two assays with confirmation test is recommended.

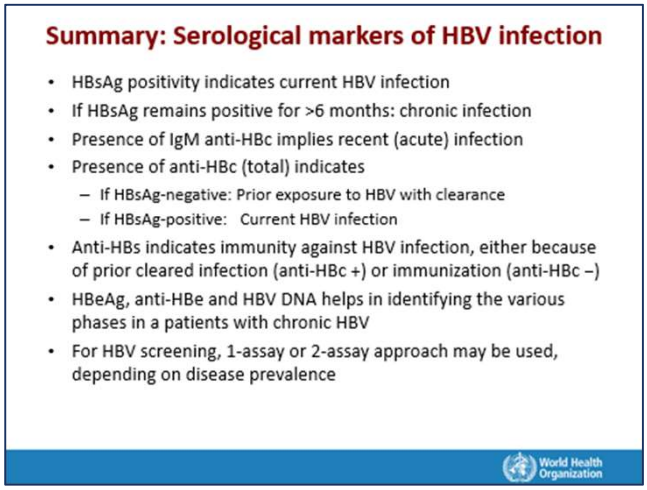
How to test for chronic HBV infection?



GUIDELINES ON HEPATITIS B AND C TESTING (WHO 2017) P53

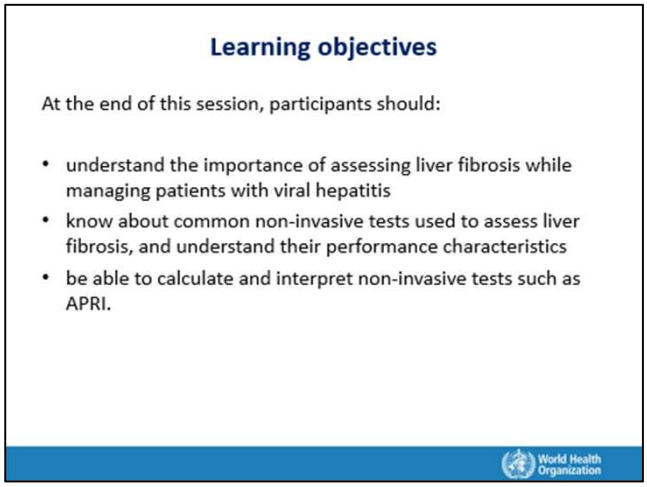
In high HBsAg seroprevalence, you should follow (A) single assay:
- After a positive result on the single HBsAg assay, patients can be diagnosed as having HBV infection and can proceed to NAT testing for their viral load (HBV DNA) testing

In low HBsAg seroprevalence, algorithm (B) with two assays is preferred:
- After positive on the first HBsAg assay, a second HBsAg assay is used for confirm infection status.
- When both tests are positive, patients are then diagnosed as having HBV infection and can proceed to NAT testing for their viral load (HBV DNA) testing

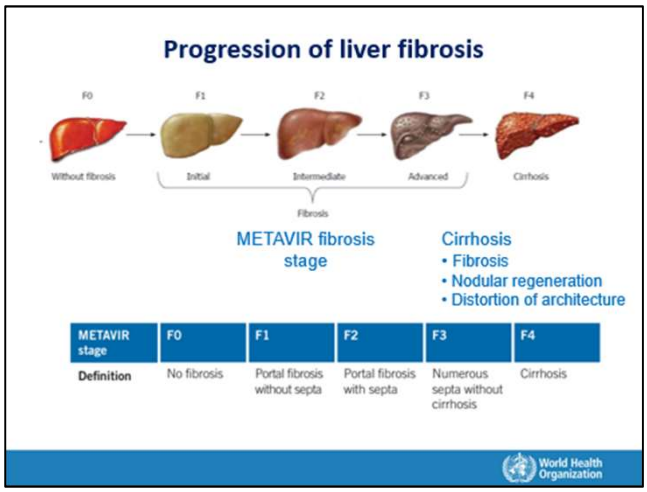

Summary: Serological markers of HBV infection
HBsAg positivity indicates current HBV infection
If HBsAg remains positive for >6 months: chronic infection
Presence of IgM anti-HBc implies recent (acute) infection
Presence of anti-HBc (total) indicates
– If HBsAg-negative: Prior exposure to HBV with clearance
– If HBsAg-positive: Current HBV infection
Anti-HBs indicates immunity against HBV infection, either because of prior cleared infection (anti-HBc +) or immunization (anti-HBc –)
HBeAg, anti-HBe and HBV DNA helps in identifying the various phases in a patients with chronic HBV
For HBV screening, 1-assay or 2-assay approach may be used, depending on disease prevalence
World Health Organization

Module 9

Non-invasive markers of chronic liver disease or liver fibrosis

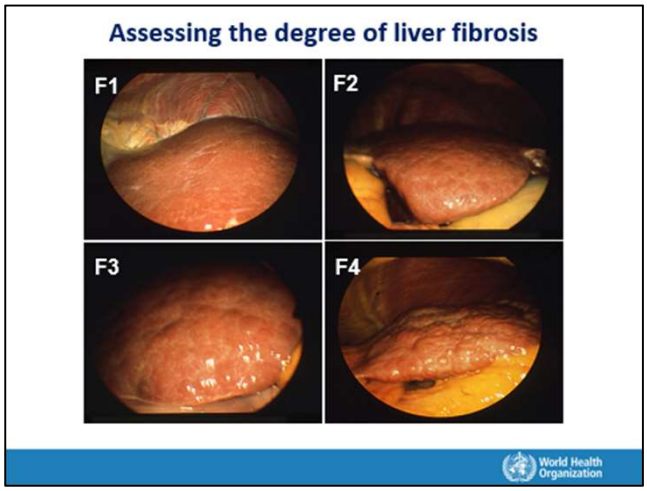


In this session we will learn about the importance of liver fibrosis, simple scores for fibrosis assessment and interpretation of these fibrosis scores.



The spectrum of liver disease ranges from minimal fibrosis to cirrhosis. Without any antiviral therapy, chronic hepatitis gradually progresses to cirrhosis in 20–30 years.

The METAVIR fibrosis staging system is a scoring system for assessing liver fibrosis based on pathological findings.



This slide shows the cirrhotic liver in a laparoscopic view. The liver suraface becomes irregular and nodular as the stage of fibrosis advances from F1 to F4.

Module 9

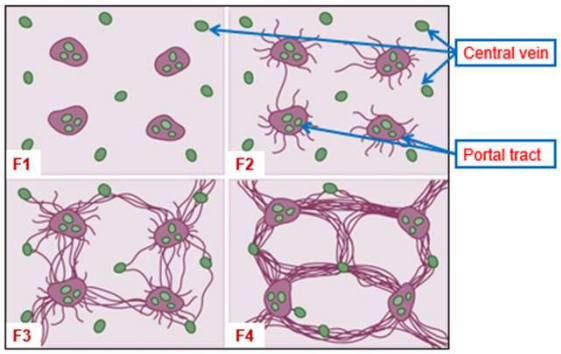
Learning objectives

At the end of this session, participants should:

- understand the importance of assessing liver fibrosis while managing patients with viral hepatitis
- know about common non-invasive tests used to assess liver fibrosis, and understand their performance characteristics
- be able to calculate and interpret non-invasive tests such as APRI.

World Health Organization

Prolonged liver injury leads to scarring (fibrosis)



Progressive laying down of scar tissue around the central vein and portal tracts

World Health Organization

Fibrosis starts around the portal area and nodules develop.
F1 indicates fibrosis in the portal area.
F2 indicates portal fibrosis with fibrous septa.
F3 indicates numerous septa without cirrhotic nodules.
F4 indicates cirrhosis, nodule formation or findings suggestive of nodule formation.

Progression of liver fibrosis

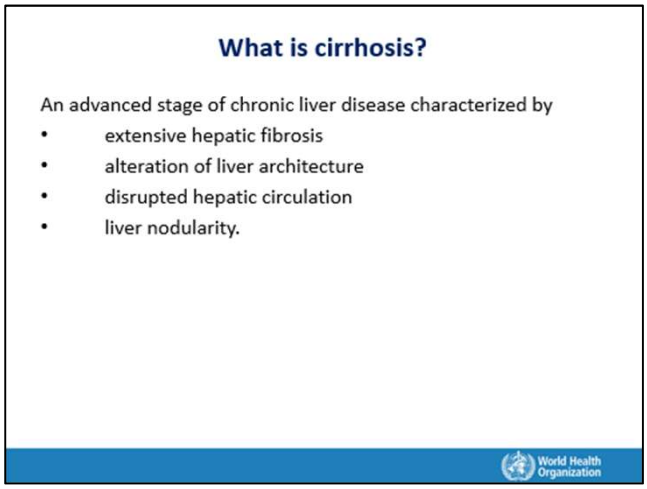
- The stages of liver fibrosis are often thought of as discrete states that occur one after the other

F1 | F2 | F3 | F4 or cirrhosis

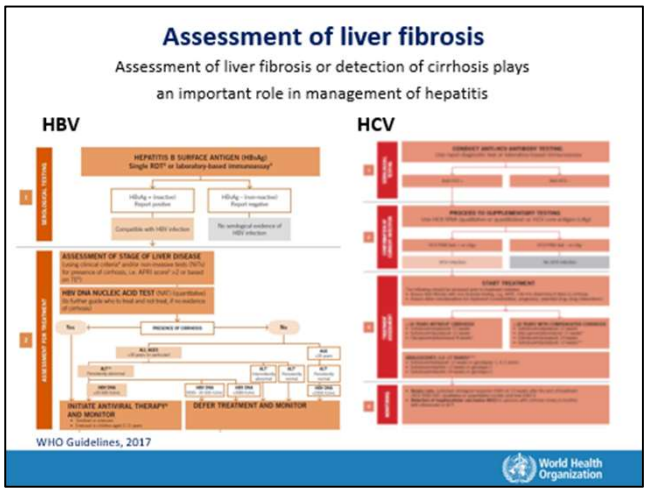
- However, in real life, fibrosis is actually a continuous and not a step-wise process (akin to the colour spectrum)

World Health Organization

The stages of liver fibrosis are often thought of as discrete states that occur one after the other. However, in real life, fibrosis is actually a continuous and not a step-wise process (akin to the colour spectrum).

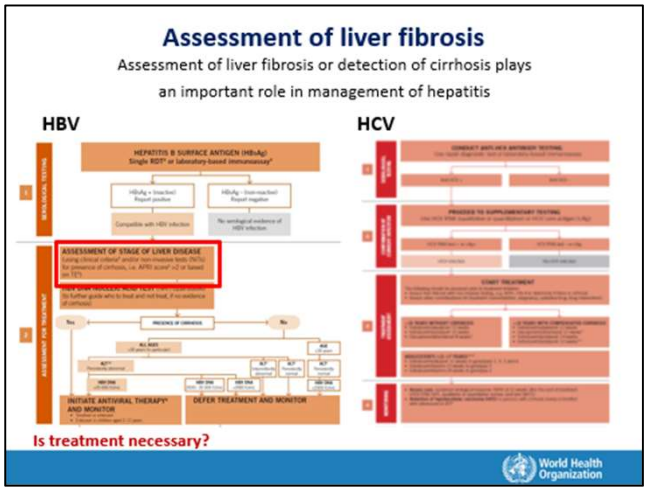


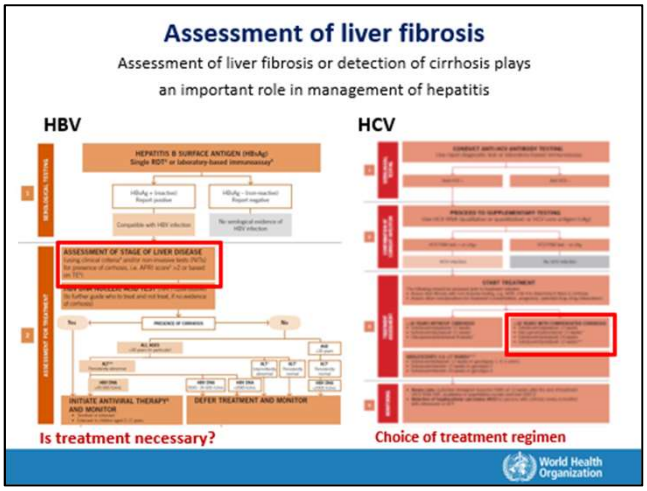
Cirrhosis is the most advanced stage of liver fibrosis, which is characterized by extensive fibrosis, altered liver microarchitecture, altered hepatic blood circulation and liver nodularity.

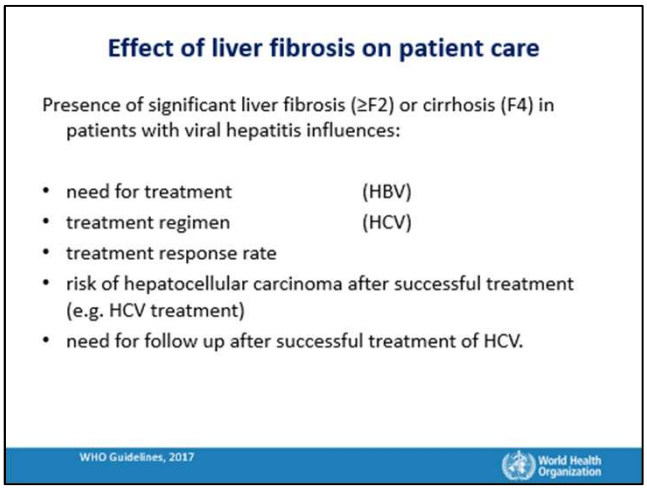


For HBV, if cirrhosis is present, initiation of antiviral treatment is recommended.

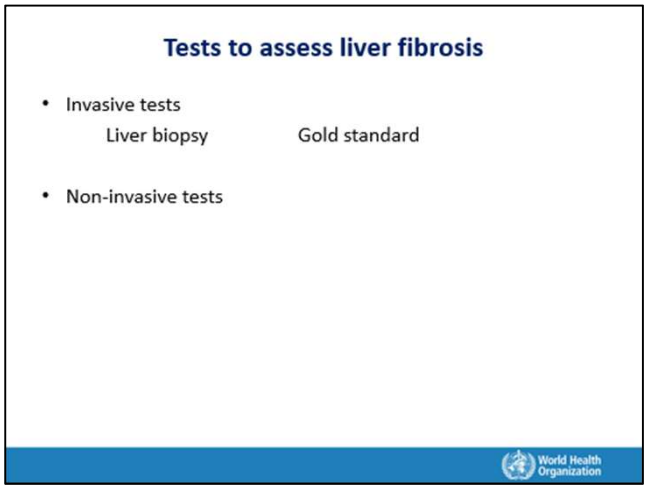
For HCV, treatment duration changes depending on the assessment of liver fibrosis.



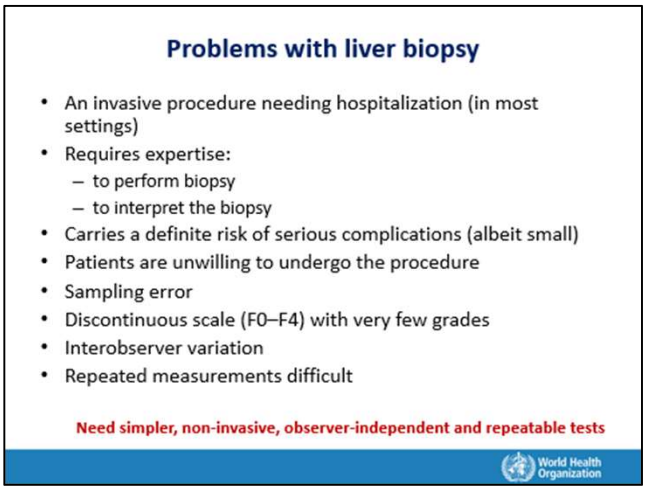




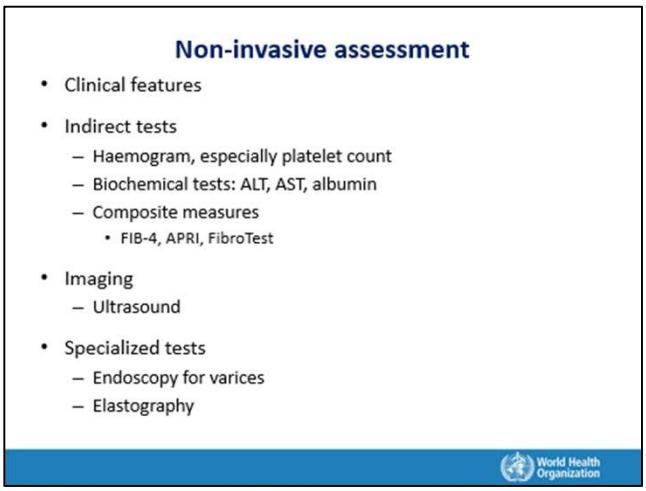
The staging of liver fibrosis influence the decision about starting treatment, selection of drugs, duration of treatment and need for follow up.



Liver biopsy is the gold standard to assess liver fibrosis and cirrhosis. Several non-invasive tests based on blood or serum indices or ultrasound principles are now available and increasingly used for evaluating liver fibrosis.

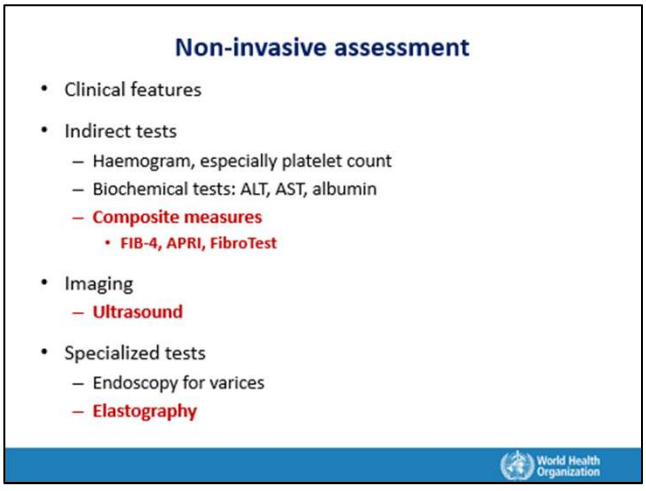


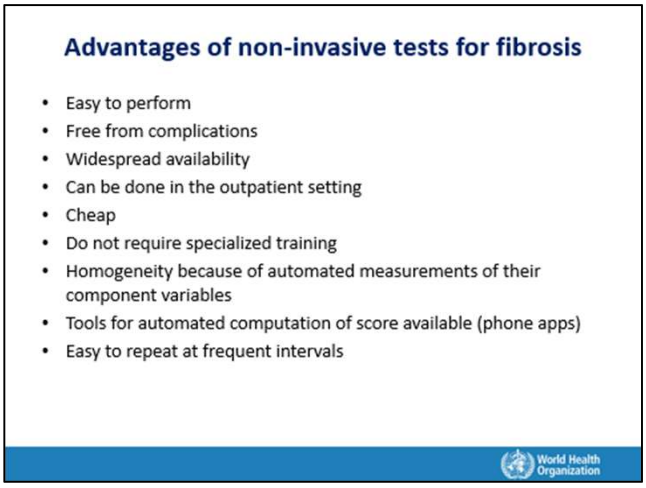
Though liver biopsy is the gold standard for assessment of liver fibrosis, it has several issues such as the highly invasive nature of the investigation with the inherent risks of complication and death, need for expertise in performing it, sampling error because of patchy distribution of fibrosis, etc. Furthermore, biopsy is a costly investigation that requires hospitalization.



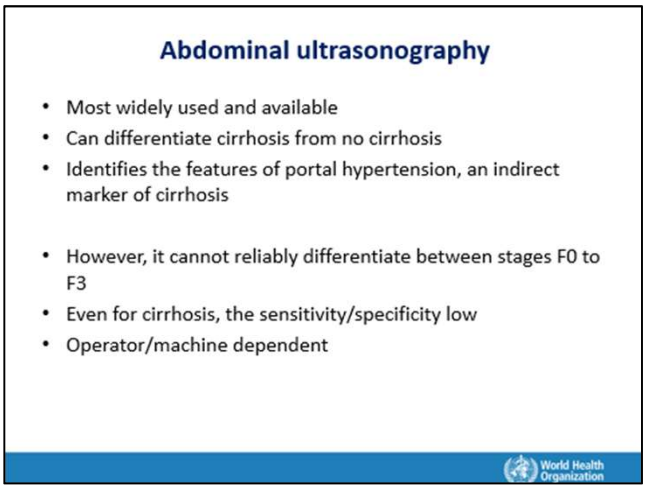
The presence of cirrhosis can be identified by a combination of clinical findings (oedema, ascites, variceal bleed, hepatic encephalopathy), haemogram (which may show pancytopenia; the platelets are the first to show a reduction in number), liver function tests (low serum albumin and composite scores such as APRI, FIB-4), ultrasound abdomen (nodular and shrunken liver, dilated portal vein, splenomegaly, etc.), and endoscopy (for oesophageal and gastric varices).

If available, liver stiffness measurement (transient elastography) could also help in diagnosing cirrhosis.

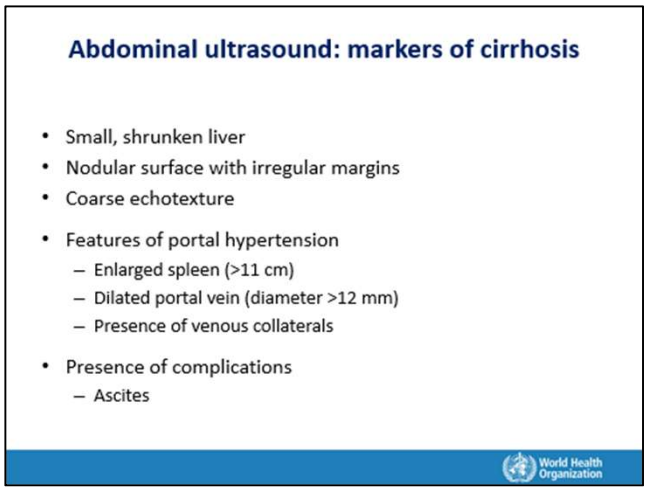




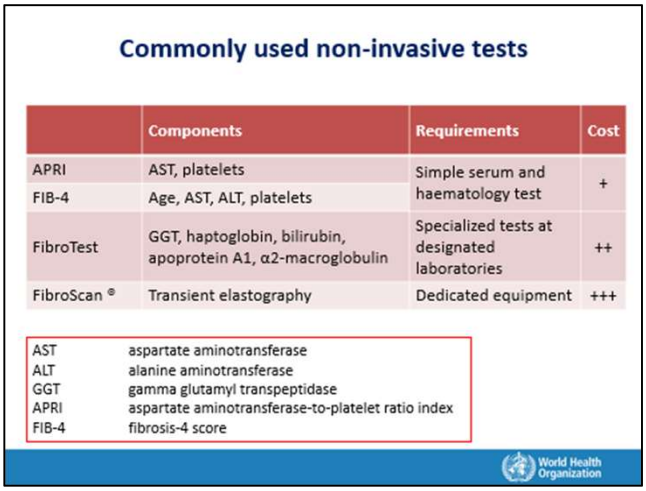
Non-invasive tests of liver fibrosis are preferred over liver biopsy because of several advantages. They are easy to perform and can be repeated, carry no risk of complication, cost less and do not need hospitalization. Furthermore, no or limited expertise is needed to perform them.



Ultrasonography (USG) of the abdomen is a widely available diagnostic test that could be efficiently used to diagnose cirrhosis. A carefully performed USG can identify the features of portal hypertension and cirrhosis. However, it cannot differentiate between the various grades of fibrosis.

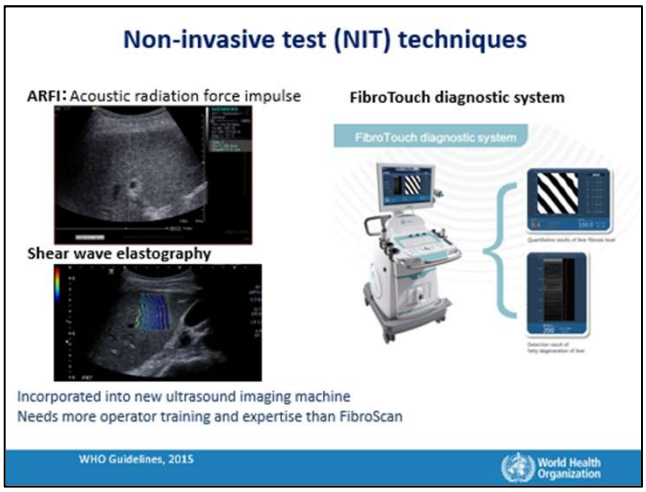


We need to train our radiologists/ultrasonographers to look for and mention on the report for the features of portal hypertension such as a small shrunken liver with a nodular surface and irregular margins, dilated portal vein, splenomegaly, ascites, etc.



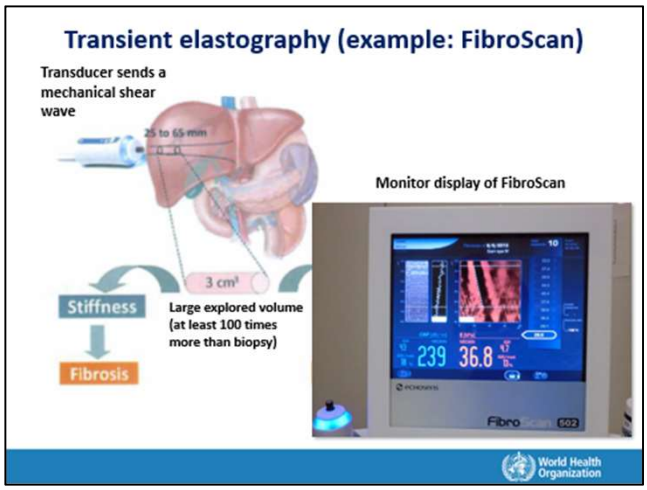
There are three common tests for assessing liver fibrosis – APRI (AST-to-platelet ratio index), FiB-4 (fibrosis-4 score) and FibroTest. As shown in this table, FibroTest needs several specific tests such as haptoglobin, A1apoprotein and alpha2-macroglobulin at designated laboratories and the test is commercially patented.

Considering the ease of calculation and accessibility, APRI is recommended as the non-invasive test of choice.

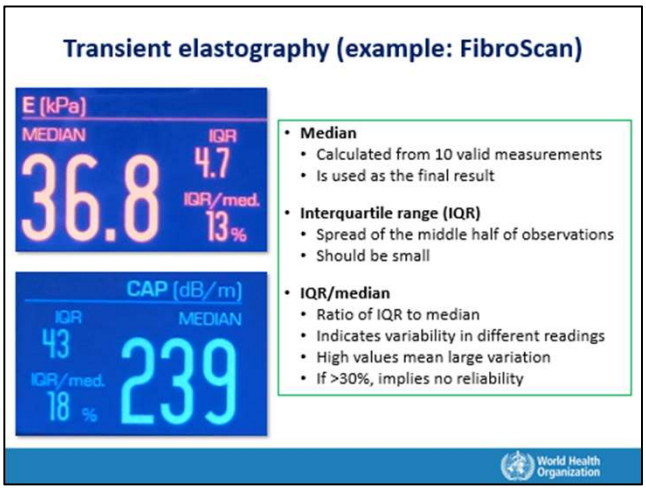


There are several other elastography techniques for assessing liver fibrosis, such as acoustic radiation force impulse (ARFI) and shear wave elastography These two are incorporated into some of the new high-end ultrasound imaging machines.

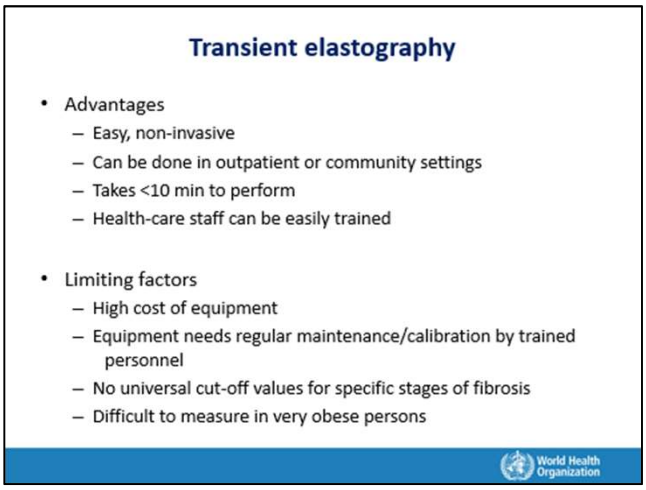
FibroTouch has been developed in China.



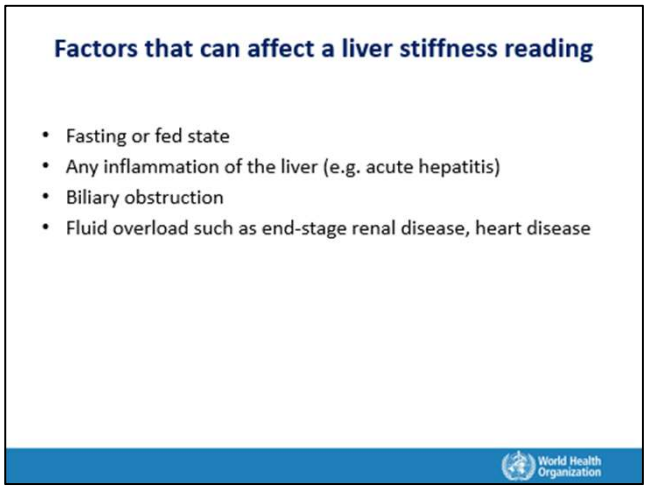
FibroScan sends a mechanical share wave from a specific transducer and measures the velocity of the wave in a relatively large volume of liver, which is at least 100 times more than biopsy. From the velocity of the wave, the liver stiffness is calculated and shown on the monitor display. The unit of measurement is kilopascal (kPa).



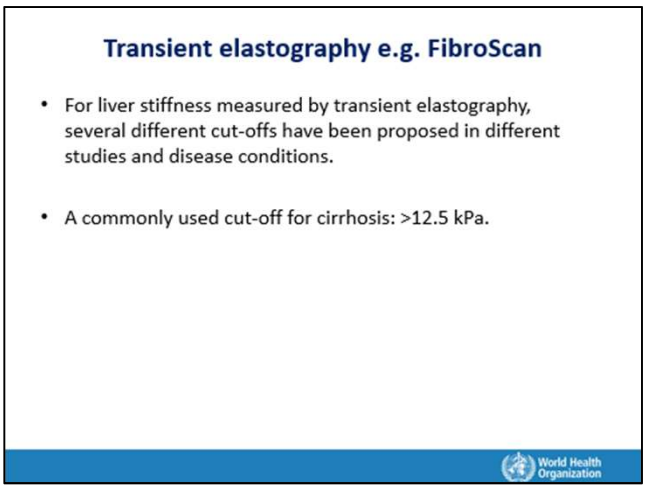
In transient elastography measurements on FibroScan, 10 measurements are taken and the median of 10 effective results is accepted as the final result. A high IQR per median indicates variation in the result. If the value of the IQR is more than 30%, the reliability of the result is questionable.



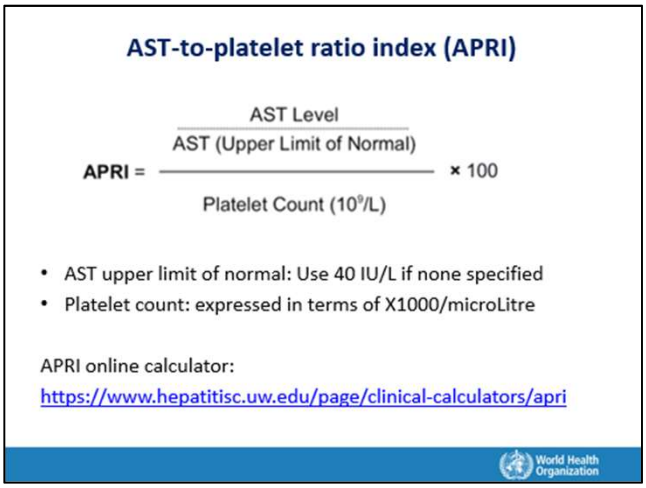
Transient elastography measurement has a few advantages and disadvantages over liver biopsy. The advantages are ease and speed of performance, and its non-invasive nature. The disadvantages are the high cost of the instrument, need for regular maintenance and inability to measure in obese people.



Liver stiffness, as measured with transient elastography, is affected by several factors such as diet, inflammation, congestion, etc. If using FibroScan, the scan should be done after 8 hours of fasting.



Though various studies have described several different cut-offs for defining cirrhosis, most of these cut-offs define cirrhosis as a value above 11–14 kPa.

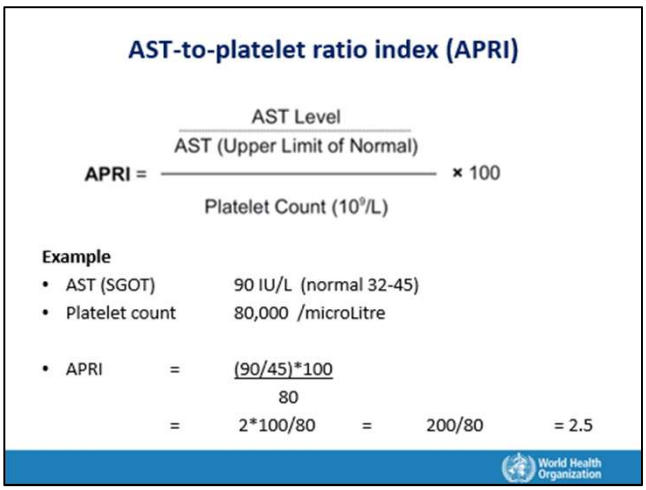


APRI means AST-to-platelet ratio index.
We can estimate liver chronicity by the AST and platelet count.

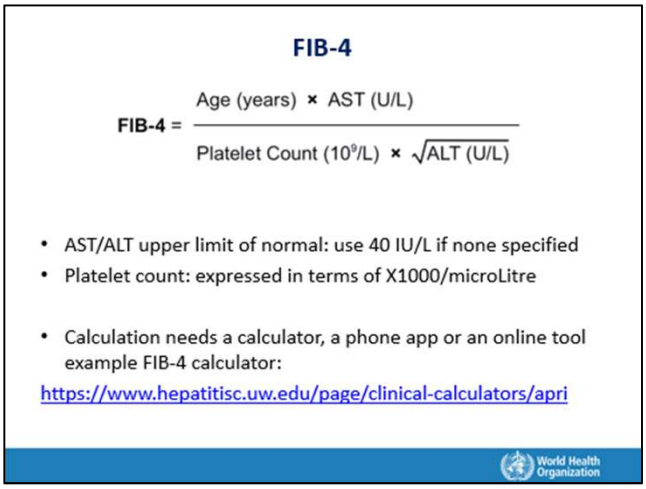
AST is divided by the AST value that is the upper limit of normal for that laboratory.

Then the result is multiplied by 100.

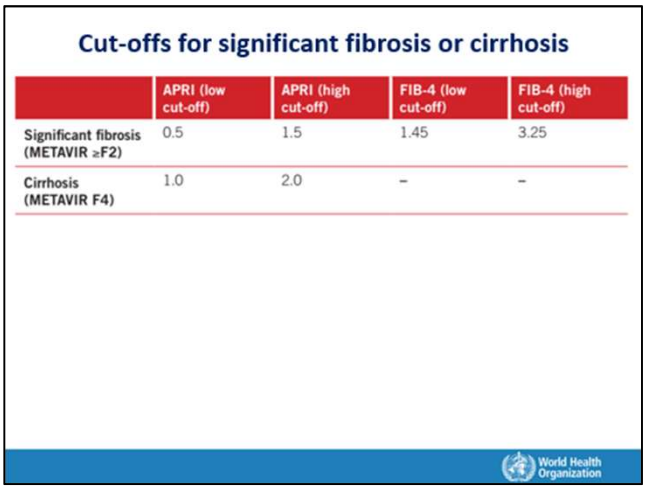
This is then divided by the platelet count.



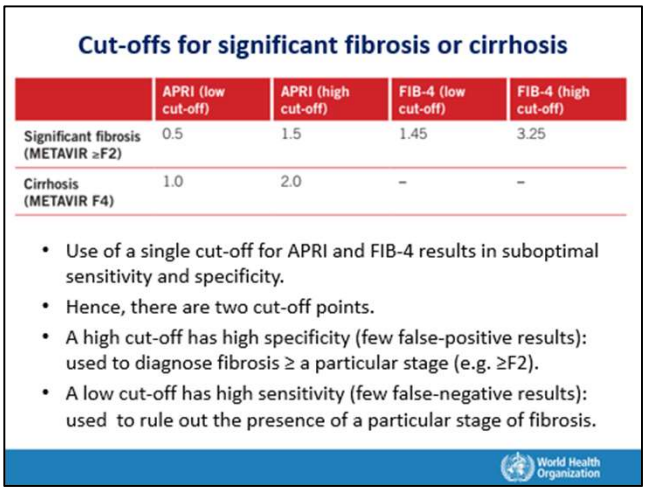
This is an example of an APRI calculation.

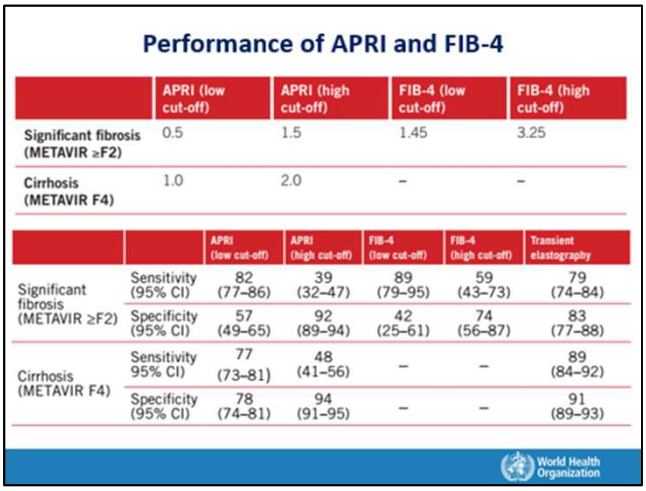


As shown in the slide, the FIB-4 score is relatively complicated and needs a calculator.



For APRI and FIB-4 indices, WHO recommends two cut-off levels to define cirrhosis: (i) A lower cut-off value, which has a high sensitivity (means it detects true positives) to detect cirrhosis if it is present and (ii) an upper cut-off value, which is more specific for diagnosing cirrhosis. Values above the high cut-off indicate a high probability of having cirrhosis; any value below the low cut-off value indicates a very low probability of having cirrhosis.





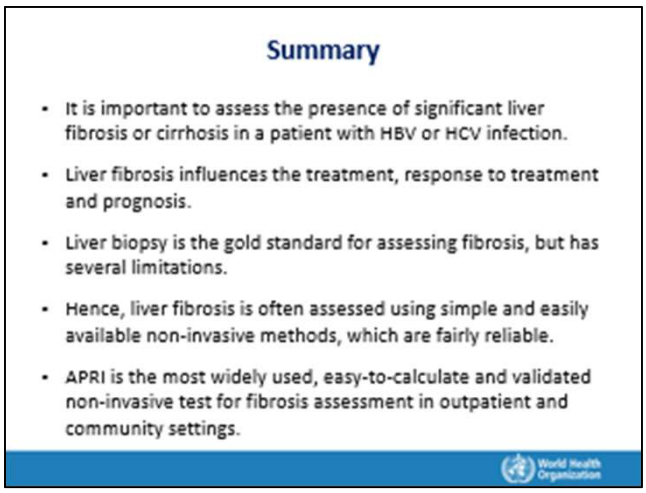
Performance of APRI and FIB-4

	APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)
Significant fibrosis (METAVIR ≥F2)	0.5	1.5	1.45	3.25
Cirrhosis (METAVIR F4)	1.0	2.0	–	–

		APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)	Transient elastography
Significant fibrosis (METAVIR ≥F2)	Sensitivity (95% CI)	82 (77–86)	39 (32–47)	89 (79–95)	59 (43–73)	79 (74–84)
	Specificity (95% CI)	57 (49–65)	92 (89–94)	42 (25–61)	74 (56–87)	83 (77–88)
Cirrhosis (METAVIR F4)	Sensitivity 95% CI)	77 (73–81)	48 (41–56)	–	–	89 (84–92)
	Specificity (95% CI)	78 (74–81)	94 (91–95)	–	–	91 (89–93)

World Health Organization

This slide shows the sensitivity and specificity of APRI and FIB-4.
If we use a high cut-off, the specificity is more than 90%.
If we use a low cut-off, the sensitivity is more than 82%



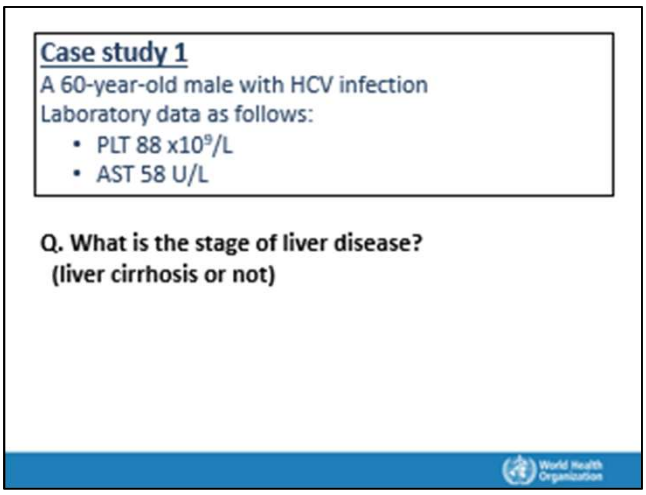
Summary

- It is important to assess the presence of significant liver fibrosis or cirrhosis in a patient with HBV or HCV infection.
- Liver fibrosis influences the treatment, response to treatment and prognosis.
- Liver biopsy is the gold standard for assessing fibrosis, but has several limitations.
- Hence, liver fibrosis is often assessed using simple and easily available non-invasive methods, which are fairly reliable.
- APRI is the most widely used, easy-to-calculate and validated non-invasive test for fibrosis assessment in outpatient and community settings.

World Health Organization

Assessment of liver fibrosis is of paramount importance in the management of patients with either HBV or HCV infection because it determines the treatment and response to treatment and prognosis.

Fibrosis is best assessed by liver biopsy though non-invasive methods are preferred and APRI is the most commonly used non-invasive method.



Case study 1

A 60-year-old male with HCV infection

Laboratory data as follows:

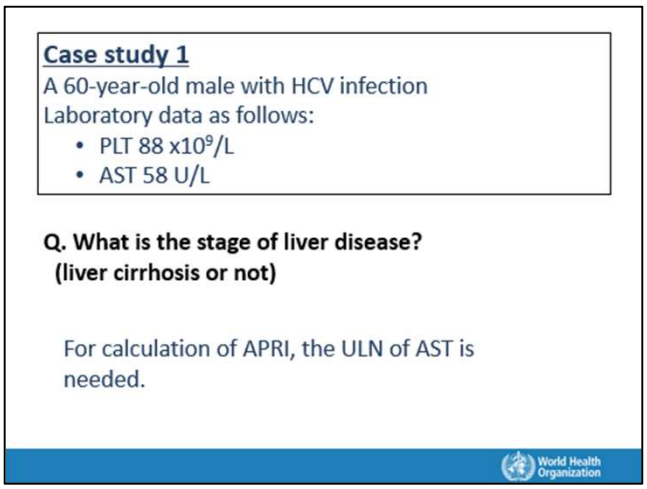
- PLT 88 x10^9/L
- AST 58 U/L

Q. What is the stage of liver disease?
(liver cirrhosis or not)

World Health Organization

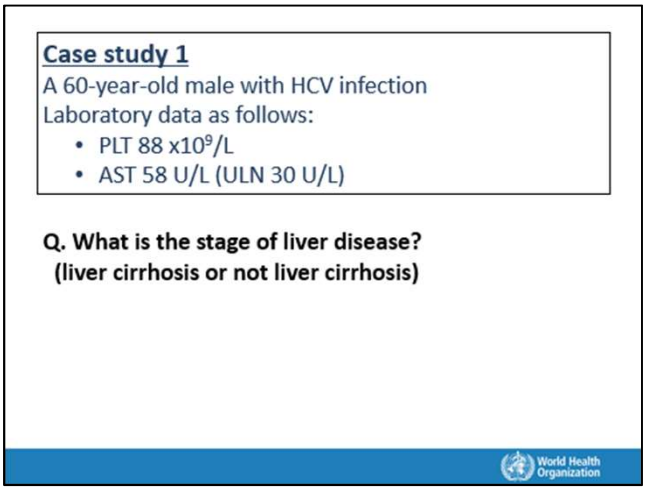
Case study 1
A 60-year-old male with HCV infection
Laboratory data as follows;
PLT 88 x10^9/L
AST 58 U/L

Question.
What is the stage of liver disease? (Liver cirrhosis or not liver cirrhosis)



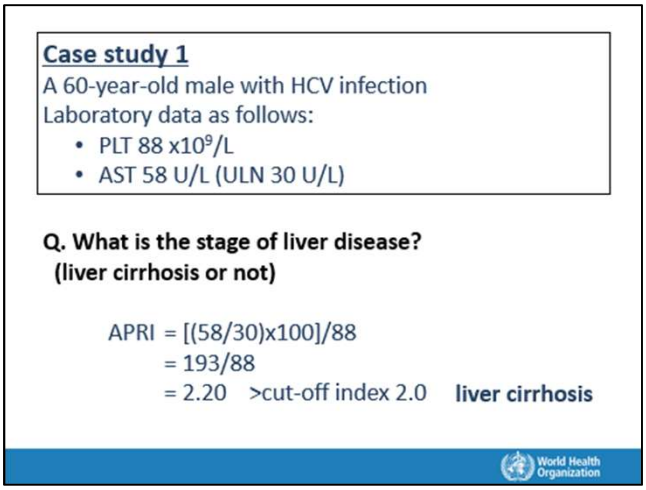
Answer:

For calculation of APRI, the ULN of AST is needed.



Upper limit of normal is 30 U/L.

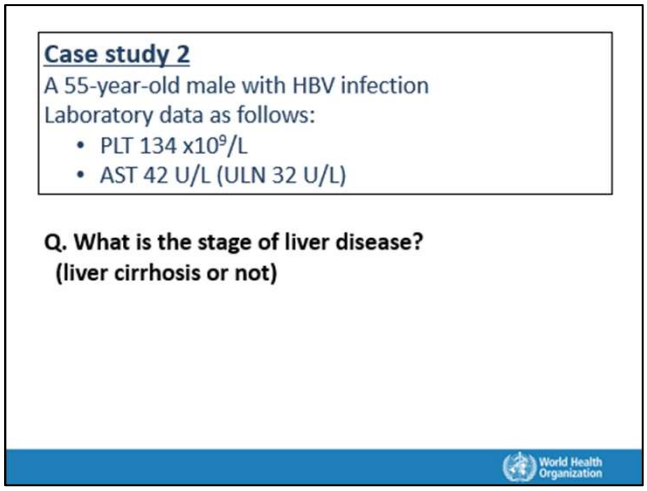
Now, you can calculate the APRI.

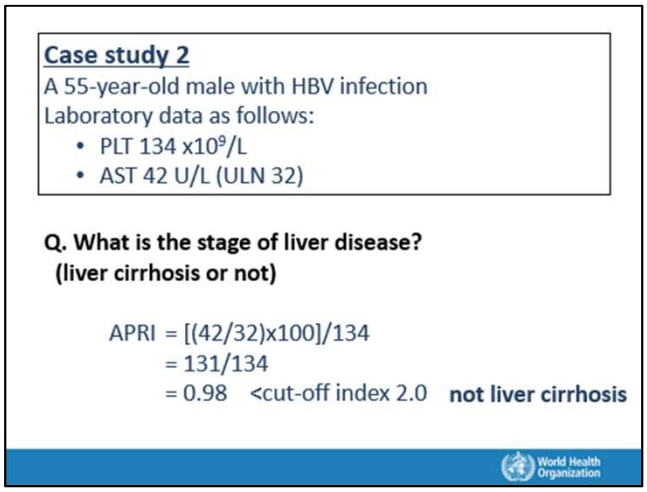


Thus,

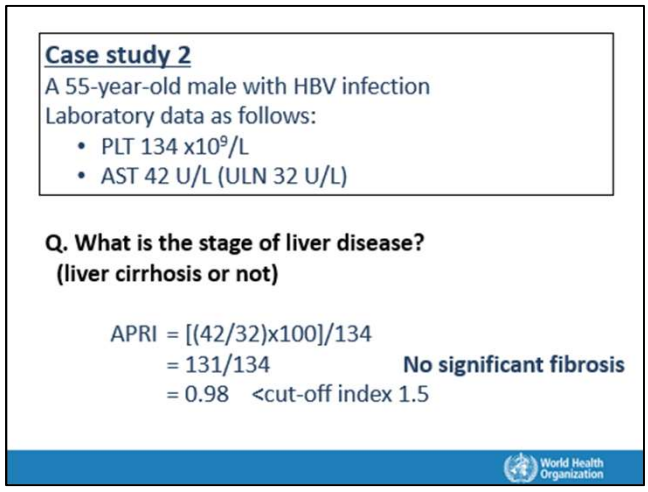
APRI is 2.20, more than the cut-off index for cirrhosis, 2.0.

So, the final diagnosis is liver cirrhosis.





Thus, the APRI is 0.98.
It is less than the cut-off index for cirrhosis, which is 2.0.
So, the final diagnosis is not cirrhosis.

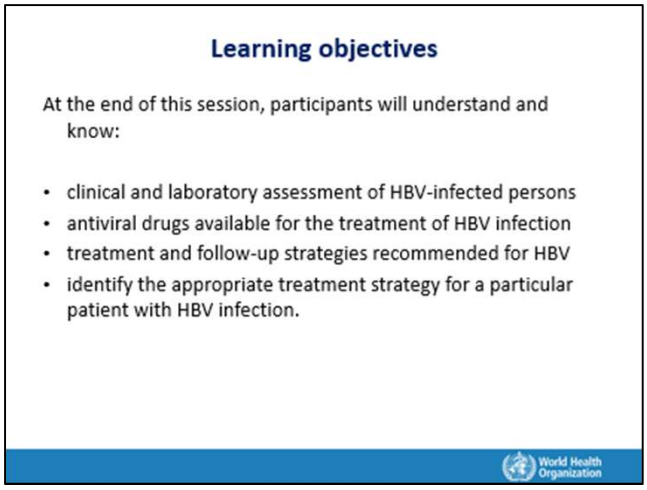


Thus, APRI is 0.98.
It is less than the cut-off index for significant fibrosis, more than F2, 1.5.
So, the final diagnosis is no significant fibrosis.

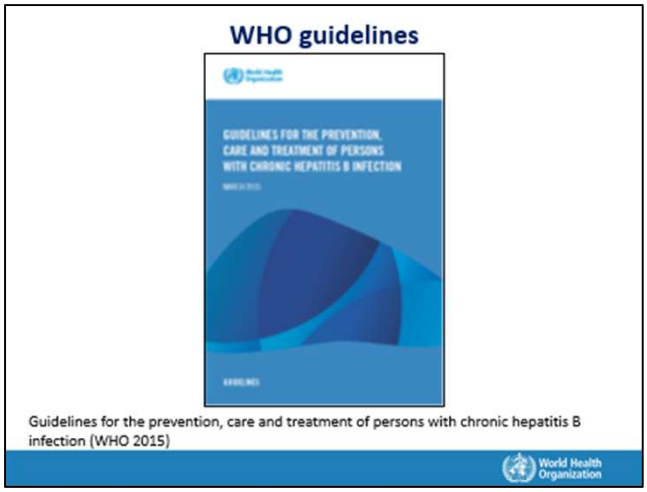
Module 10

Clinical management of hepatitis B virus infection

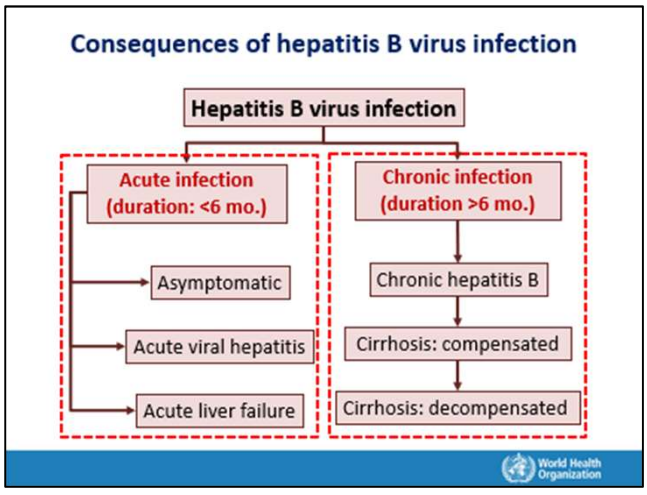
Module 10



At the end of this session, we shall be able to assess a patient by clinical examination and laboratory investigation. We shall also be able to plan the appropriate management of the patient.



This session is based on the WHO HBV guidelines launched in 2015.

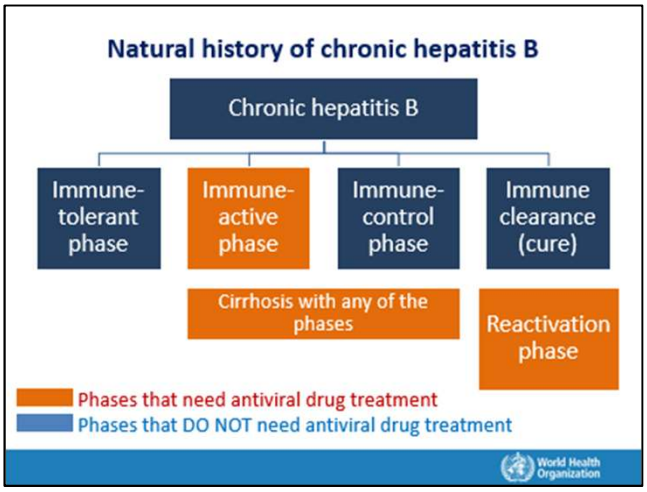


Once HBV infection is established in a host, the clinical illness may take one of two possible courses: first, acute infection and second, chronic infection.

The probability of developing acute or chronic infection is primarily determined by the age of the host at the time of infection (already discussed). Acute infection is characterized by marked elevation of serum levels of liver enzymes. These patients clear the virus in six months of time. Chronic infection remains asymptomatic and such patients fail to clear the virus. A person with acute HBV infection may either remain asymptomatic or develop features of acute viral hepatitis or may progress to acute liver failure.

In a person with chronic HBV infection, the liver is constantly exposed to virus-induced injury. After decades of virus-induced liver injury and natural healing with fibrosis, progression to liver cirrhosis may occur.

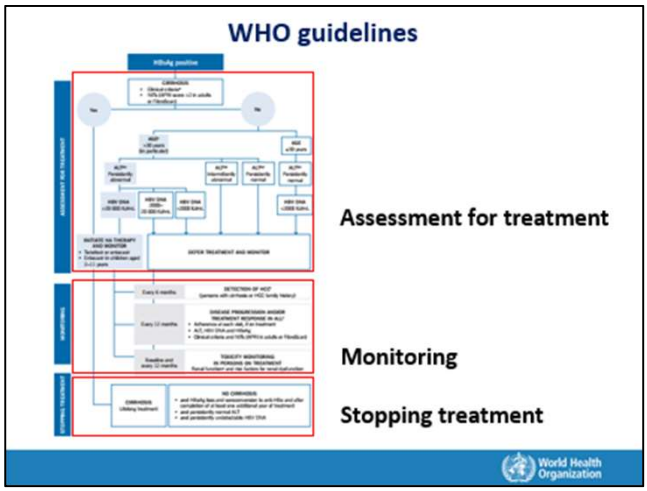
If cirrhosis is left unchecked for a long time, patients may develop the complications of cirrhosis, such as ascites, variceal bleed and hepatic encephalopathy (called as decompensation).



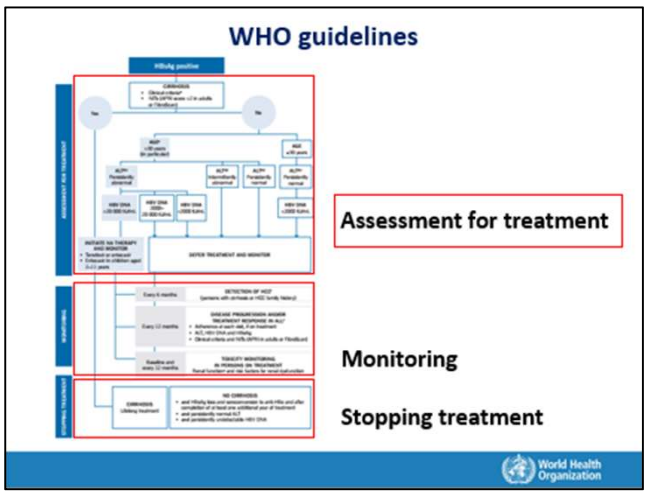
Our target is chronic HBV infection.

The natural history of chronic hepatitis is shown in this slide. There are basically 4 phases, immune-tolerant phase, immune-active phase, immune-control phase and immune clearance or cure phase. Another phase is the reactivation phase, which occurs in specific situations.

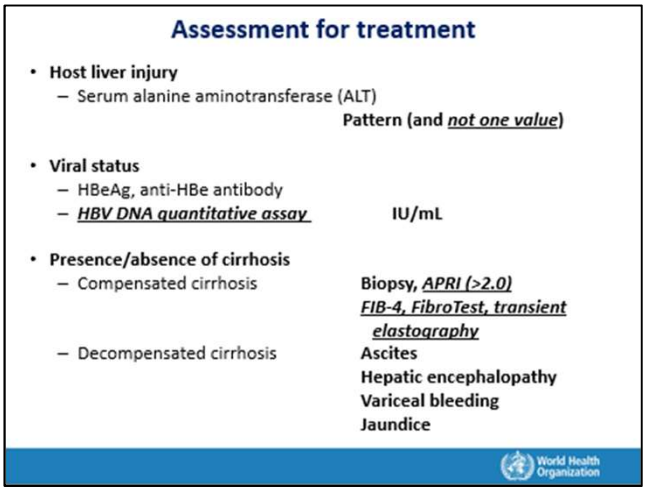
The orange-coloured phases need antiviral drug treatment: the immune-active phase, cirrhosis and reactivation phase. The other phases do not need antiviral drug treatment.



This is the algorithm from the WHO HBV guidelines. It is in three parts – assessment for treatment, monitoring and stopping treatment.



This is the algorithm from the WHO HBV guidelines. It is in three parts – assessment for treatment, monitoring and stopping treatment.

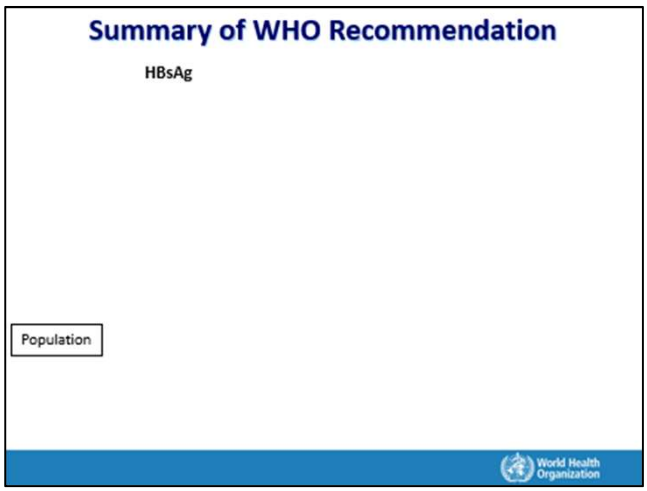


Before starting treatment, the person should be evaluated for host liver injury, viral status and presence or absence of cirrhosis.

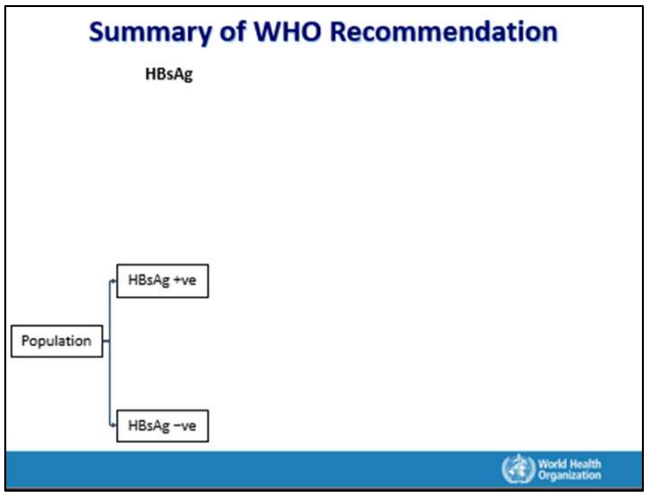
Host liver injury is assessed with the temporal pattern of serum levels of alanine aminotransferase or ALT. We need to check the patterns of ALT. Hence, we rely on several values of ALT tested at an interval of 3–4 months. The serum ALT pattern is described as persistently normal, persistently abnormal or intermittently abnormal.

Next, to assess the virus activity, we need to do a HBV DNA quantitative assay. If you cannot do an HBV DNA quantitative assay, you can use HBeAg and anti-HBe antibody.

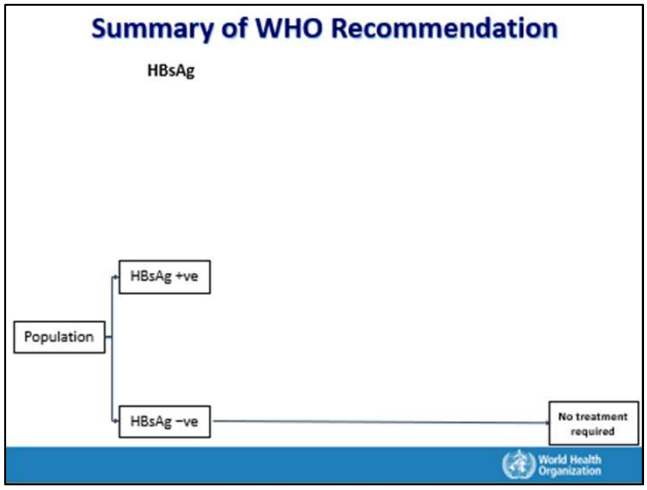
Finally, we assess for the presence or absence of cirrhosis. For the assessment of compensated cirrhosis, liver biopsy is the gold standard but invasive. Non-invasive tests, such as APRI, FIB-4, Fibrotest, transient elastography (e.g. FibroScan) are used. Clinical symptoms such as ascites, hepatic encephalopathy, variceal bleeding and jaundice indicate decompensated cirrhosis. If the HBV DNA is reported in copies, divide it by 5 get the value in IU.



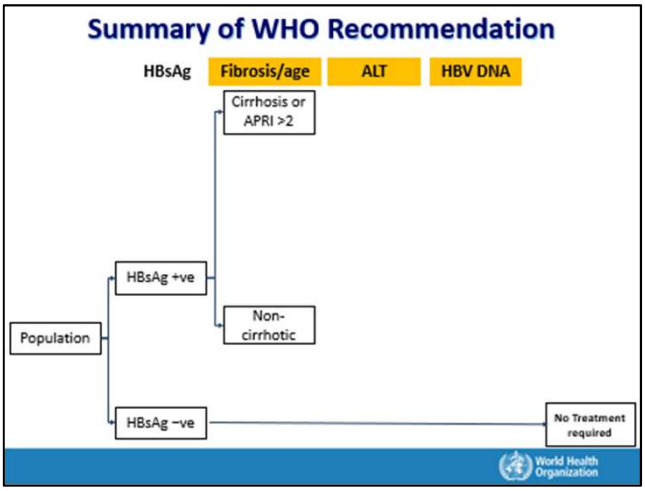
- HBsAg is used as a screening test.



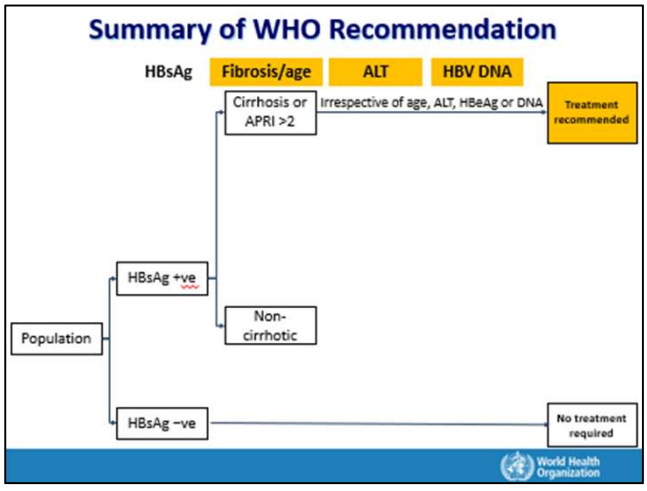
- In case of HBsAg-negative persons, what should you do?



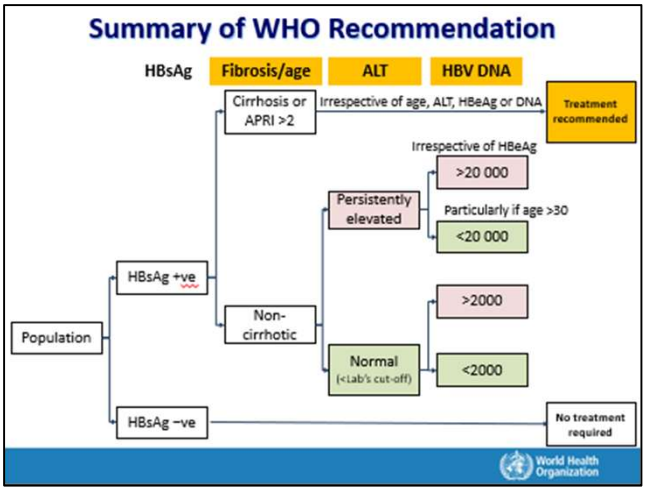
- In the case of an HBsAg-negative person, no treatment is required because there is no infection with HBV.



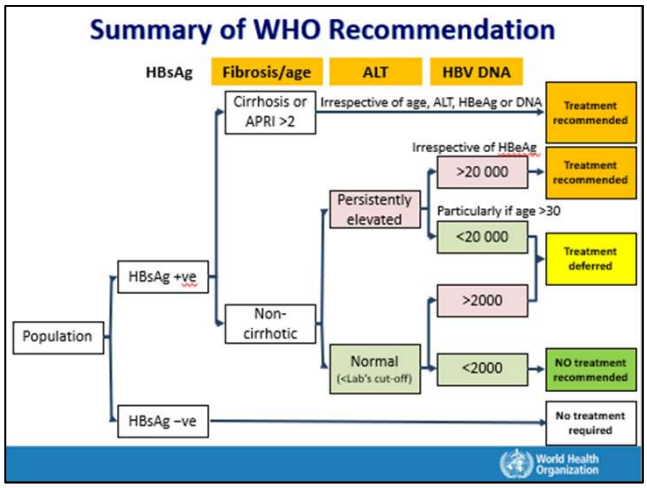
- In case of an HBsAg-positive person, you must assess for the presence or absence of cirrhosis.
- For assessment of cirrhosis, the APRI score is convenient and cirrhosis is present if the score is more than 2.
- Of course, other assessments for cirrhosis also show the presence of cirrhosis.
- What should you do?



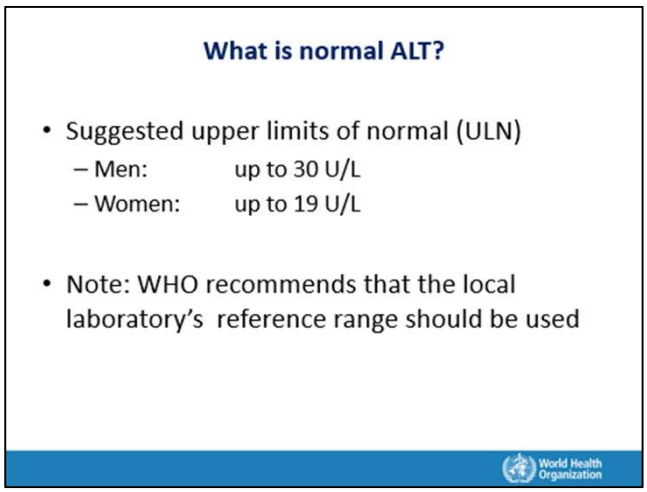
- In case of cirrhosis, all infected persons should be treated, irrespective of age, ALT, HBeAg or DNA.



- In case of non-cirrhotic persons, you should assess the pattern of ALT to see if it is persistently elevated or normal.



- In case of a non-cirrhotic person, if the ALT is persistently elevated and HBV DNA is more than 20 000 IU/L, treatment is recommended.
- But if the HBV DNA is less than 20 000 IU/L, treatment is deferred.
- If the ALT is normal and HBV DNA is less than 2000 IU/L, no treatment is recommended.
- If the ALT is normal and HBV DNA is more than 2000 IU/L, treatment is deferred.



- What is normal ALT?
- Usually, normal ALT means a value that is lower than the upper limit of normal (ULN).
- For men, it is 30 U/L, for women, 19 U/L.
- Note - WHO recommends that the local laboratory's reference range be used.

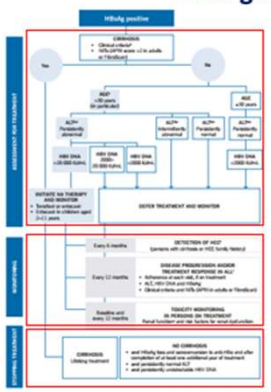
What is a persistently normal/elevated ALT?

- Three ALT determinations below or above the upper limit of normal
- Made at unspecified intervals during a 6–12-month period or at predefined intervals during a 12-month period

World Health Organization

- Next, what is a persistently normal or elevated ALT?
- These are usually interpreted as three ALT determinations that are below or above the upper limit of normal.
- The three are measured at unspecified intervals during a 6–12-month period or at predefined intervals during a 12-month period.

WHO guidelines



Assessment for treatment

Monitoring

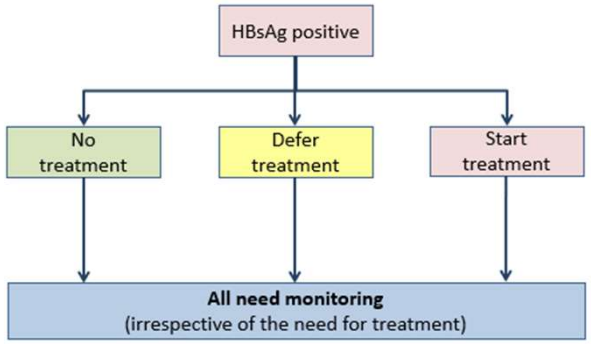
Stopping treatment

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (WHO 2015) p. xxvi

World Health Organization

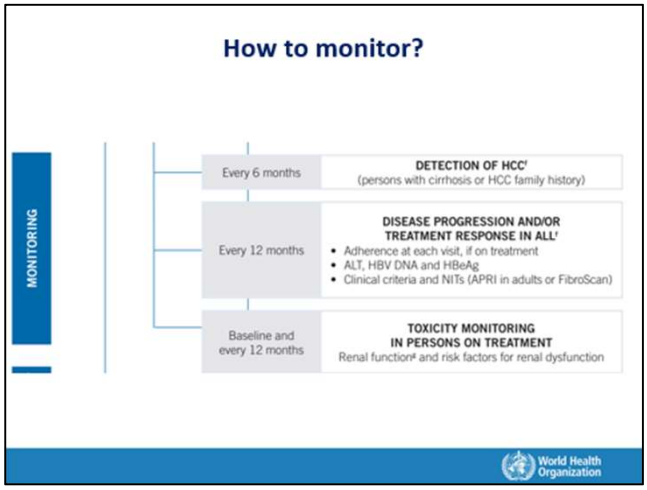
- Next, we come to monitoring of a person who was initially evaluated.

Need for monitoring

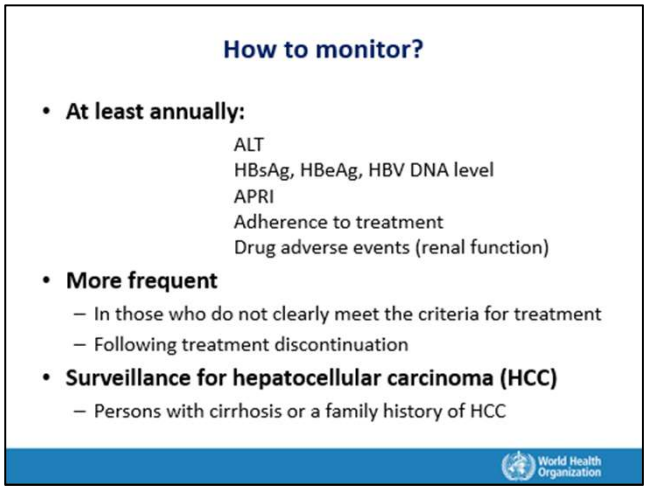


World Health Organization

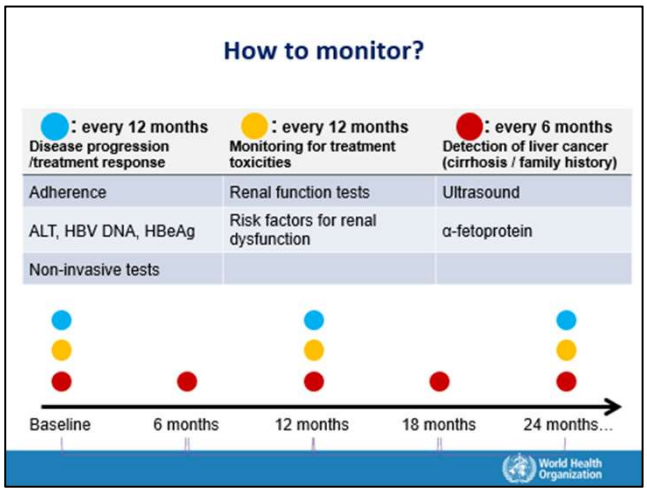
- All persons who are HBsAg positive need monitoring irrespective of the need for treatment.
- You can easily understand the need for monitoring after starting treatment, that is, to look for efficacy, toxicity and development of cancer.
- In case of deferred treatment or even no treatment, ALT, HBV DNA and onset of cancer should be monitored to avoid missing a change in chronic HBV infection status and disease progression.



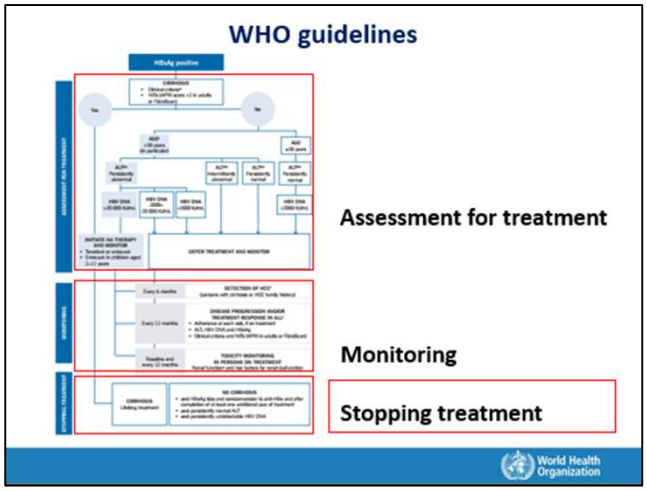
- How to monitor?
- In the WHO HBV guidelines, monitoring is divided to three parts, detection of HCC, disease progression and/or treatment response in all, and toxicity monitoring in persons on treatment.



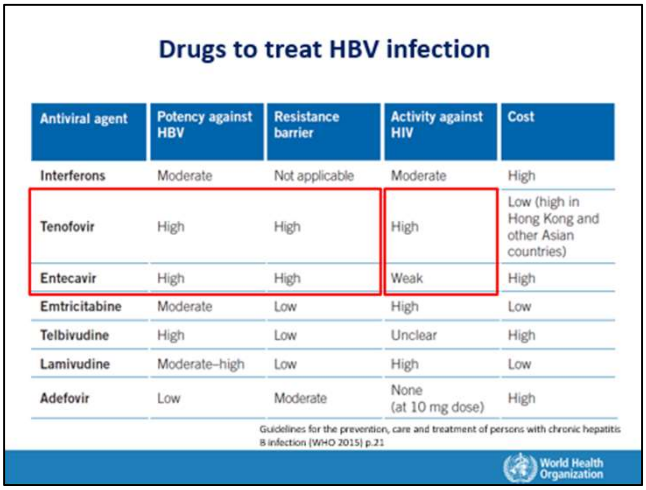
- At least annually, the following should be monitored: ALT, HBsAg, HBeAg, HBV DNA level, APRI, adherence to treatment and drug adverse events, renal functions.
- In those who do not clearly meet the criteria for treatment, i.e. treatment-deferred cases, or in those following treatment discontinuation, more frequent monitoring is recommended.
- Six-monthly monitoring for surveillance of hepatocellular carcinoma (HCC) is recommended for persons with cirrhosis or a family history of HCC.



- This is a visualized figure for monitoring.
- As shown by the blue circles, in all persons with HBV infection, ALT, HBV DNA or HBeAg, non-invasive tests and treatment adherence should be monitored every 12 months.
- As shown by the yellow circles, in persons on treatment, renal function tests and risk factors for renal dysfunction should be monitored every 12 months.
- As shown by the red circles, in persons with cirrhosis or a family history of HCC, ultrasound and alpha-fetoprotein, which is a tumour marker for HCC, should be monitored every 6 months.



This is the algorithm from the WHO HBV guidelines. We will now talk about stopping treatment



Antiviral agent	Potency against HBV	Resistance barrier	Activity against HIV	Cost
Interferons	Moderate	Not applicable	Moderate	High
Tenofovir	High	High	High	Low (high in Hong Kong and other Asian countries)
Entecavir	High	High	Weak	High
Emtricitabine	Moderate	Low	High	Low
Telbivudine	High	Low	Unclear	High
Lamivudine	Moderate–high	Low	High	Low
Adefovir	Low	Moderate	None (at 10 mg dose)	High

This table shows the drug that can be used to treat HBV infection as given in the WHO HBV guidelines.

There are 7 drugs to treat HBV infection ranging from interferons to adefovir. Of these drugs, tenofovir or entecavir is recommended as first-line antiviral treatment.

These two drugs have a high potency against HBV and a high resistance barrier.

The difference between them is activity against HIV. Tenofovir is highly active against HIV, but entecavir is weakly active against HIV.

WHO recommendation: choice of drug

- ***In all adults, adolescents and children aged 12 years or older*** in whom antiviral therapy is indicated, nucleos(t)ide analogues that have a high barrier to drug resistance (***tenofovir or entecavir***) are recommended.
- ***Entecavir*** is recommended in ***children.***

World Health Organization

WHO recommends the following choice of drug:
In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, nucleos(t)ide analogues that have a high barrier to drug resistance (tenofovir or entecavir) are recommended.

Entecavir is recommended in children.

Drug dose

- Adults Entecavir 0.5 mg/day orally
  (1.0 mg/day for decompensated cirrhosis)
  Tenofovir 300 mg/day orally
- Children need dose modification

Drug	Dose	
Tenofovir (in children 12 years of age and older, and weighing at least 35 kg)	300 mg once daily	
Entecavir (in children 2 years of age or older and weighing at least 10 kg. The oral solution should be given to children with a body weight up to 30 kg)	Recommended once-daily dose of oral solution (mL)	
	Body weight (kg)	Treatment-naive persons[a]
	10 to 11	3
	>11 to 14	4
	>14 to 17	5
	>17 to 20	6
	>20 to 23	7
	>23 to 26	8
	>26 to 30	9
	>30	10

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (WHO 2015) p.55

World Health Organization

The dose in adults of entecavir is 0.5 mg/day orally, and tenofovir is 300 mg/day orally.

In case of decompensated cirrhosis, entecavir 1.0 mg/day is recommended. In case of children, an oral solution of entecavir can be used for children 3 years of age or older and weighting at least 10 kg.

As shown in this table, the dose of entecavir oral solution is adjusted according to the body weight.

Drugs need dose adjustment in renal disease

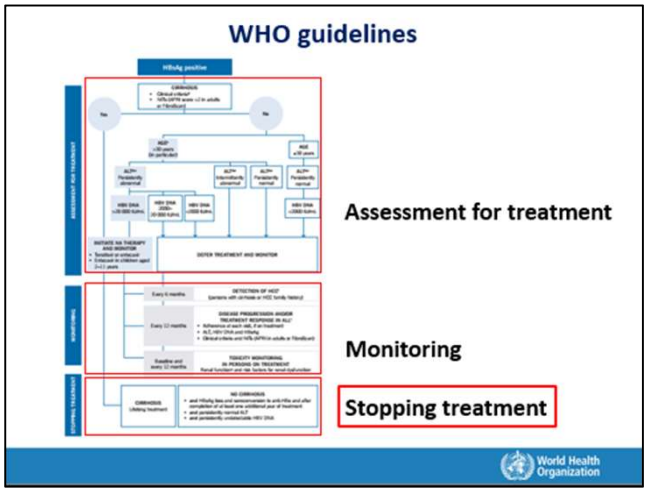
Drug	Recommended dose reduction or dosing interval			
	CrCl (mL/min)[b]			
	≥50	30–49	10–29	<10, Haemodialysis or CAPD
Tenofovir[a,b]	One 300 mg tablet every 24 hours (7.5 scoops of powder every 24 hours)	One 300 mg tablet every 48 hours (or 160 mg [3 scoops] of powder every 24 hours)	One 300 mg tablet every 72–96 hours (or 60 mg [1.5 scoops] of powder every 24 hours)	Every 7 days or one 300 mg tablet following completion of approximately every 12 hours of dialysis (or 20 mg [0.5 scoops] of powder following completion of approximately every 12 hours of dialysis)
Entecavir	0.5 mg once daily[c]	0.25 mg once daily OR 0.5 mg every 48 hours	0.15 mg once daily OR 0.5 mg every 72 hours	0.05 mg once daily OR 0.5 mg every 7 days
Entecavir (decompensated liver disease)	1 mg once daily	0.5 mg once daily OR 1 mg every 48 hours	0.3 mg once daily OR 1 mg every 72 hours	0.1 mg once daily OR 1 mg every 7 days

World Health Organization

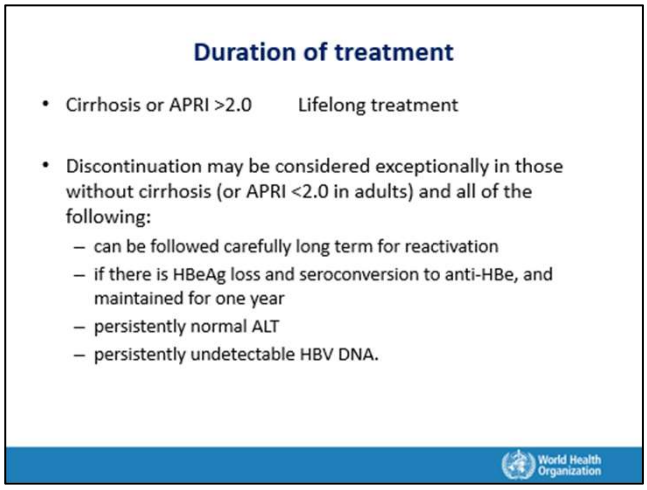
The dose of tenofovir and entecavir should be adjusted if there is renal disease.

As shown in this table, in case the creatine clearance is less than 50 mL/min, the dose of tenofovir or entecavir should be reduced to half or administered every 48 hours.

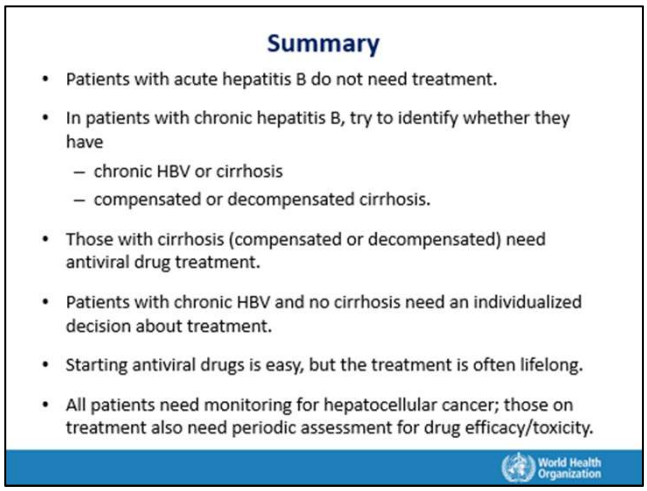
The dose reduction recommended varies according to the renal function, as shown in this table.



Next, we will talk about stopping treatment.



- In case of cirrhosis or APRI more than 2.0, usually you cannot stop treatment and the treatment should continue lifelong.
- Discontinuation may be considered exceptionally in those without cirrhosis or APRI less than 2.0 in adults and all of the following criteria:
    - those who can be followed carefully long term for reactivation
    - if there is HBeAg loss and seroconversion to anti-HBe, and maintained for one year
    - those whose ALT is persistently normal
    - those in whom HBV DNA is persistently undetectable.
- These are very limiting situations and basically treatment should continue lifelong.

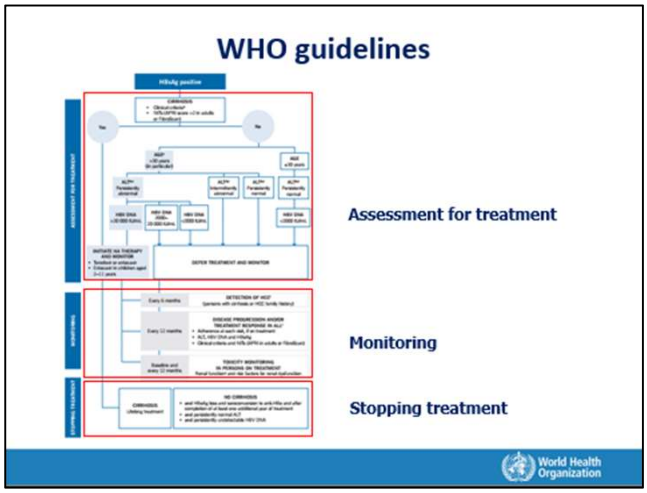


- Patients with acute HBV usually recover completely and clear HBsAg in six months of time.
- All those with chronic HBV should be assessed for the presence of cirrhosis.
- All those with cirrhosis need antiviral drugs.
- Among those without cirrhosis, antiviral drugs are needed for a small proportion of people.
- All chronic HBV patients, whether on treatment or not, need lifelong monitoring at regular intervals.

Module 11

Clinical management of hepatitis B virus infection: case studies

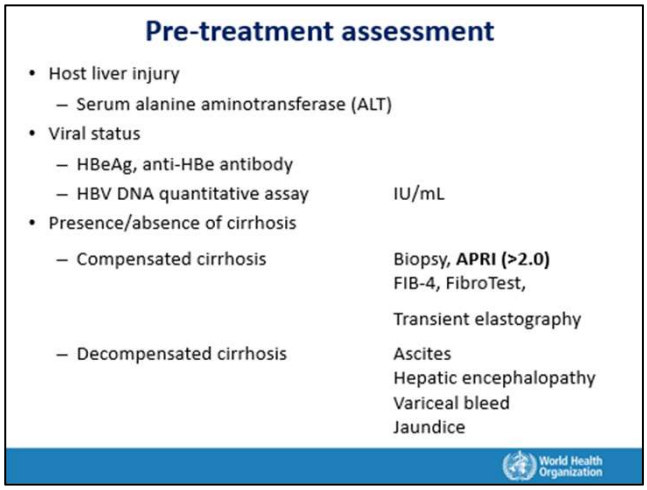
Module 11



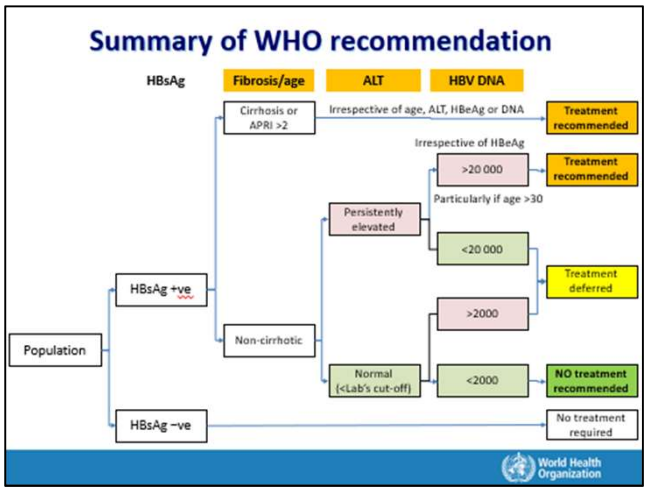
The decision to initiate antiviral therapy is usually based on an assessment of the stage of liver disease.

Persons with chronic hepatitis B (CHB) need follow up and monitoring before, during and after discontinuation of antiviral therapy.

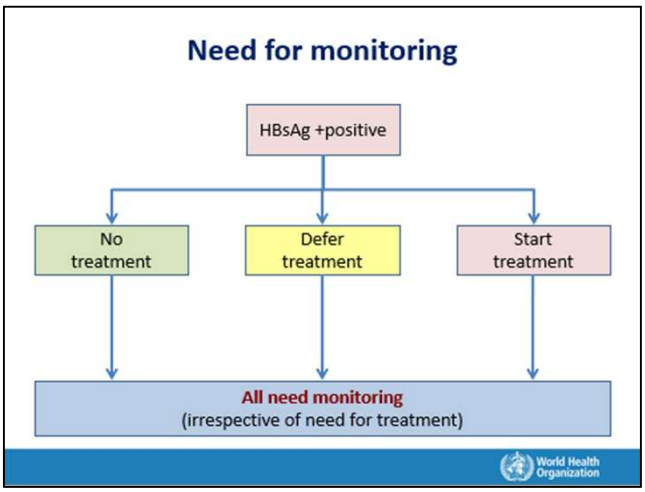
We are first going to re-cap some important concepts



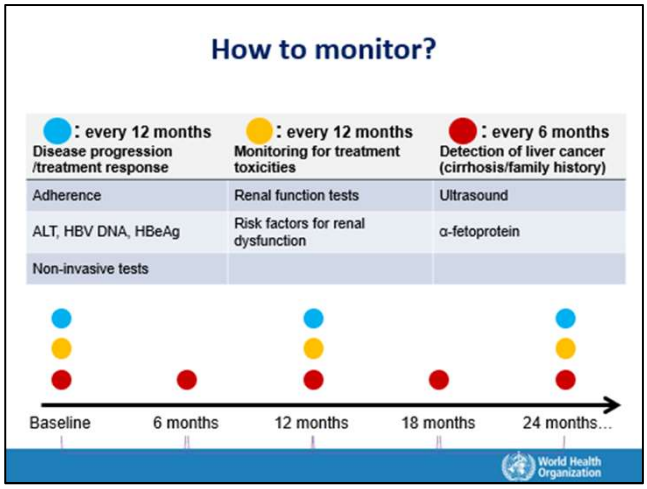
- Before starting treatment, the person should be evaluated for host liver injury, viral status and presence or absence of cirrhosis.
- Host liver injury is assessed with the temporal pattern of serum level of alanine aminotransferase (ALT).
- We need to check the patterns of ALT. Hence, we rely on several values of ALT tested at an interval of 3–4 months. Serum ALT patterns are described as persistently normal, persistently abnormal or intermittently abnormal.
- Next, to assess the virus activity, we need to do an HBV DNA quantitative assay. If you cannot perform an HBV DNA quantitative assay, you can use alternatively HBeAg and anti-HBe antibody.
- Finally, we assess for the presence or absence of cirrhosis.
- For the assessment of compensated cirrhosis, liver biopsy is the gold standard but invasive. Non-invasive tests such as APRI, FIB-4, FibroTest and transient elastography (e.g. FibroScan) are used.
- Clinical symptoms such as ascites, hepatic encephalopathy, variceal bleeding and jaundice indicate decompensated cirrhosis.



The decision to initiate antiviral therapy is based on an assessment of fibrosis, serum ALT and HBV DNA.



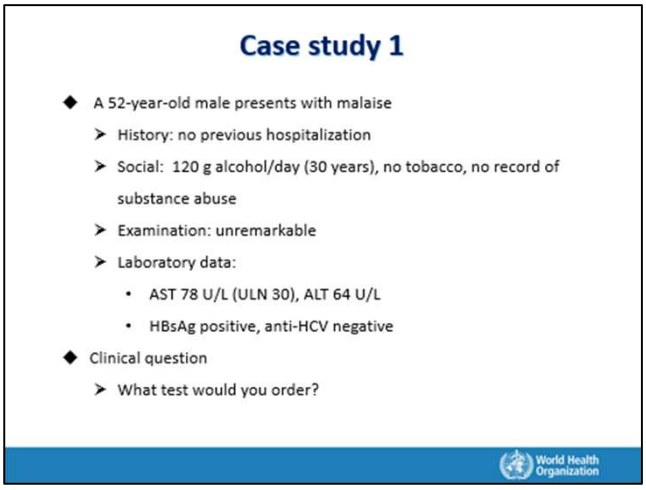
Chronic hepatitis B is a dynamic disease, and persons with CHB need follow up and monitoring before, during and after discontinuation of antiviral therapy for disease progression and development of HCC, treatment response and toxicities. Prior to treatment, the goal of monitoring is to identify the phase of disease, change in phase and progression of disease. It helps to decide the appropriate timing for treatment initiation.



While on treatment, monitoring is required to assess treatment adherence, status of virus replication (with HBV DNA or HBeAg), progression of liver fibrosis, development of features of portal hypertension and HCC. The Guidelines Development Group therefore recommended at least annual monitoring of ALT, HBeAg (for seroconversion [to anti-HBe]) and HBV DNA levels (where testing is available), and also non-invasive tests of fibrosis such as APRI to assess for progression to cirrhosis.

HBV genotyping and resistance testing are not required to guide therapy.

More frequent and careful monitoring was recommended conditionally based on limited evidence in the following groups: those with more advanced disease (compensated or decompensated cirrhosis) because the risk of HCC is reduced but not eliminated with treatment, and their higher risk of adverse events; during the first year of treatment to assess treatment response; where adherence to therapy is a concern; and after stopping therapy.



A middle-aged man presented with non-specific symptoms and was tested and found to be HBsAg positive. His ALT and AST were mildly elevated. He consumes alcohol regularly for a long period of time.

How would you investigate this person?

Case study 1

- What test would you order?
  - HBV DNA 2.8 x10^8 IU/mL, HIV rapid diagnostic test negative
  - Hb 11.8 g/dL, neutrophils 2.5 x10^9/L, PLT 98 x10^9/L
  - Alb 3.4 g/dL, T-Bil 1.2 mg/dL, PT-INR 1.6
  - Creatinine 1.0 mg/dL
  - Ultrasound: chronic liver disease, mild splenomegaly
- Clinical question
  - What is the stage of liver disease?
  - Is treatment recommended?
  - What monitoring does she require?

World Health Organization

Investigations revealed a low platelet count, deranged LFT, high HBV DNA and features of chronic liver disease on USG abdomen.

With this information we need to decide about the stage of liver disease, whether he has liver fibrosis, the need for antiviral drugs and our follow-up plan.

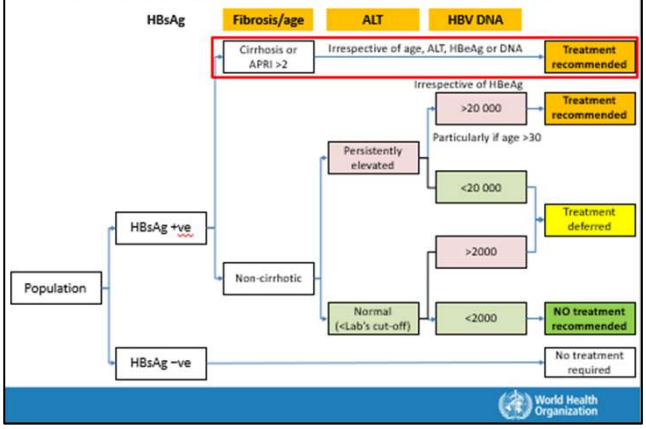
Case study 1: answers

- What is the stage of liver disease?
  - APRI 2.6; [78/30]x100/98 >2.0; liver cirrhosis (compensated)
- Is treatment recommended?
  - Diagnosis: liver cirrhosis B
  - Select recommended preferred regimen:
    - ✓ Tenofovir 300 mg once daily or entecavir 0.5 mg once daily
    - ✓ Lifelong treatment
  - Assist for treatment: stop alcohol intake
- What monitoring does she require?
  - Monitor for efficacy and toxicity (baseline and every 12 months)
  - Lifelong screening for HCC (every 6 months)

World Health Organization

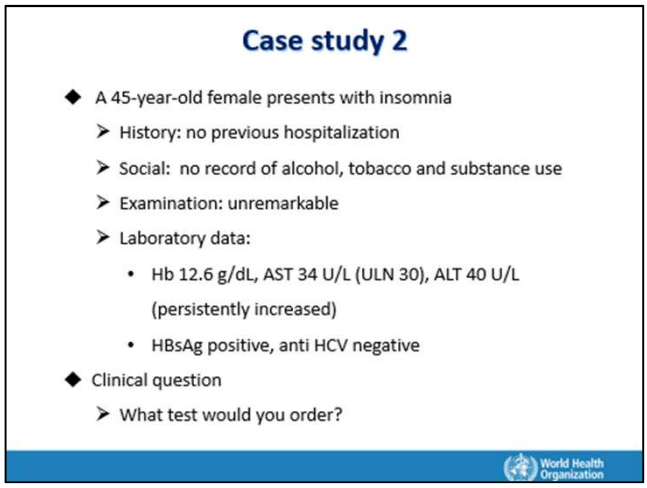
On calculation, APRI is more than 2, which indicates the presence of cirrhosis. For a patient with cirrhosis with any level of detectable HBV DNA, treatment with an antiviral drug is indicted. The drugs of choice are tenofovir or entecavir, which has to be continued for life. All such patients will need follow up every six-monthly for compliance, toxicity, complications of portal hypertension and HCC.

Summary of WHO recommendation

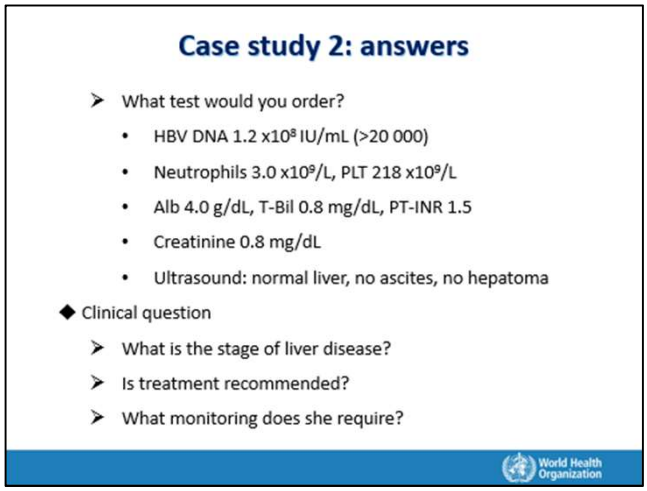


World Health Organization

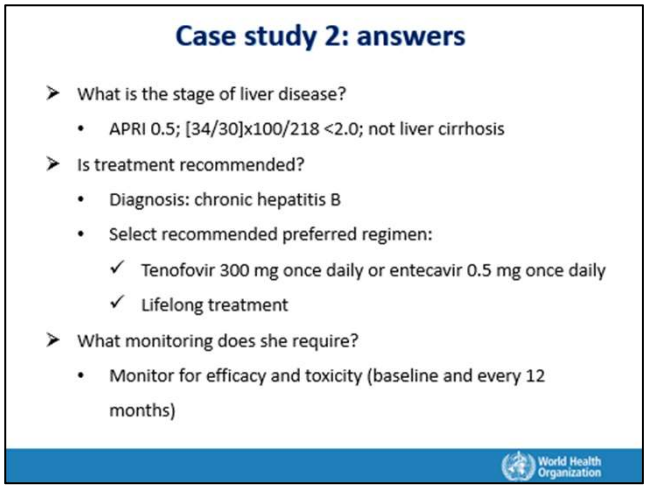
This is the flow chart that we learnt in the last session and at the top of it we can see the status of our first patient who requires treatment in view of cirrhosis and detectable HBV DNA.



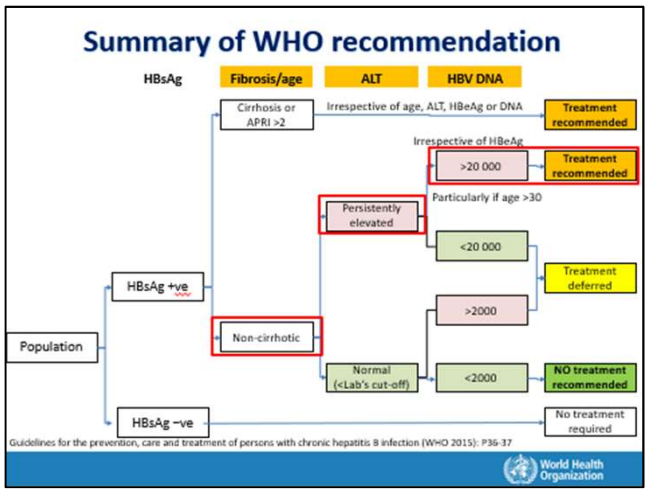
A 45-year-old lady presented with insomnia and was found to be HBsAg positive on routine work-up. Her ALT is elevated. We need to evaluate this lady.



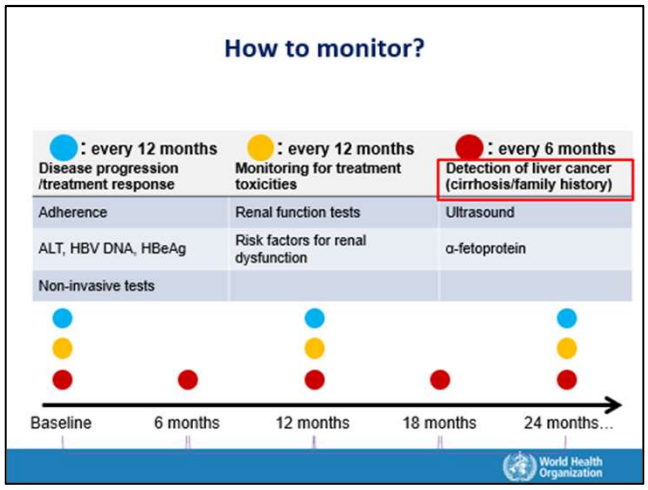
Her LFT and USG abdomen were normal. Her HBV DNA was high. With this information we need to decide about the stage of liver disease, liver fibrosis, need for antiviral drugs and our follow-up plan.



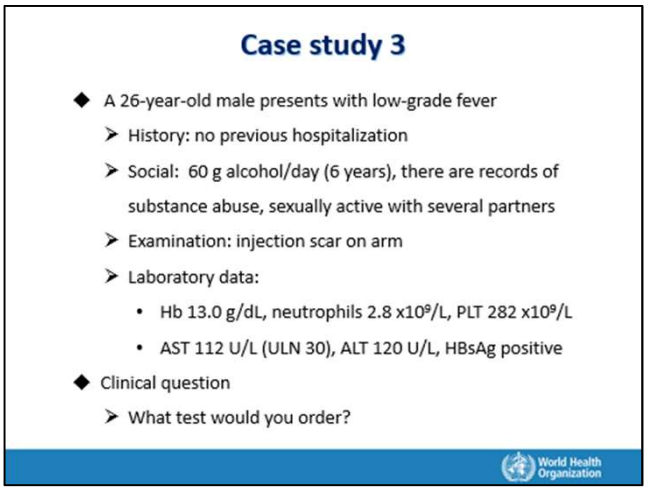
Her APRI is 0.5 hence she does not have cirrhosis. In view of the elevated ALT, she will need antiviral treatment and we can choose between entecavir and tenofovir.



In this flowchart, we can see the status of our present patient who requires treatment in view of the elevated ALT and high DNA.



The WHO Guidelines recommended at least annual monitoring of ALT, HBeAg (for seroconversion [to anti-HBe]) and HBV DNA levels (where testing is available), and also non-invasive tests of fibrosis such as APRI to assess for progression to cirrhosis. We need to monitor every 6-monthly for HCC with USG and alpha-fetoprotein.



A 26-year-old young male with multiple risk factors for hepatitis B. His ALT and AST were elevated threefold. What next?

Case study 3: answers

- What test would you order?
  - HBV DNA 3.5 x10^8 IU/mL (>20 000)
  - Alb 4.1 g/dL, T-Bil 1.0 mg/dL, PT-INR 1.4
  - Creatinine 0.8 mg/dL
  - Anti-HCV negative, HIV RDT negative
  - Ultrasound: normal liver, no ascites, no hepatoma
- Clinical question
  - What is the stage of liver disease?
  - Is treatment recommended?
  - What monitoring does he require?

World Health Organization

He has high HBV DNA without any evidence of cirrhosis on USG. Such persons should always be screened for HIV.

Case study 3: answers

- What is the stage of liver disease?
  - APRI 1.3; [112/30]x100/282 <2.0; not liver cirrhosis
- Is treatment recommended?
  - Diagnosis: chronic hepatitis B
  - Select recommended preferred regimen:
    - ✓ Tenofovir 300 mg once daily or entecavir 0.5 mg once daily
    - ✓ Lifelong treatment
  - Assist for treatment: alcohol sobriety, drug abstinence
- What monitoring does he require?
  - Monitor for efficacy and toxicity (baseline and every 12 month)

World Health Organization

APRI was <2 and hence he had no cirrhosis. Liver enzymes were elevated and DNA was high. So, the patient qualifies for antiviral drugs. Besides antiviral drugs, the management of such people should also be focused on rehabilitation such as drug deaddiction, etc.

Case study 4

- 52-year-old man
- Planned for laparoscopic cholecystectomy
- Detected to have HBsAg positive on evaluation
- History
  - no previous hospitalization
  - no addiction
- Examination: unremarkable

What tests would you order?

World Health Organization

A 52-year-old person was planned for laparoscopic cholecystectomy and was incidentally detected to have HBV infection during preoperative work-up.

How would you evaluate this person?

Case study 4: test results

Investigations	Values
Haemoglobin (g/dL)	11.8
Platelets (x 10^9/L)	98
Total bilirubin (mg/dL)	1.2
Albumin (g/dL)	3.4
ALT (IU/L) AST (IU/L)	66 (<40 IU/L) 98 (<40 IU/L)
Prothrombin time (INR)	1.6
HBV DNA (IU/L)	1120
USG abdomen	Coarse echo-texture of liver Portal vein diameter = 14 mm Splenomegaly, no ascites

World Health Organization

His liver enzymes were elevated, HBV DNA was low but USG abdomen showed features of chronic liver disease or cirrhosis.

Case study 4: issues in management

- What is the stage of liver disease?
  - *Cirrhosis versus no cirrhosis*
  - *Compensated versus decompensated*
- Is treatment recommended?
  - *What drug?*
  - *How long?*
- How would you monitor the person during treatment?

World Health Organization

These are the question we need to answer for this patient before starting antiviral drugs.

Case study 4: questions

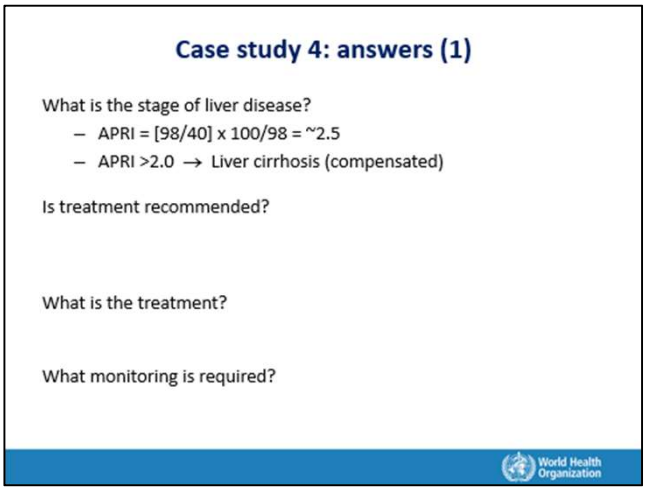
What is the stage of liver disease?

Is treatment recommended?

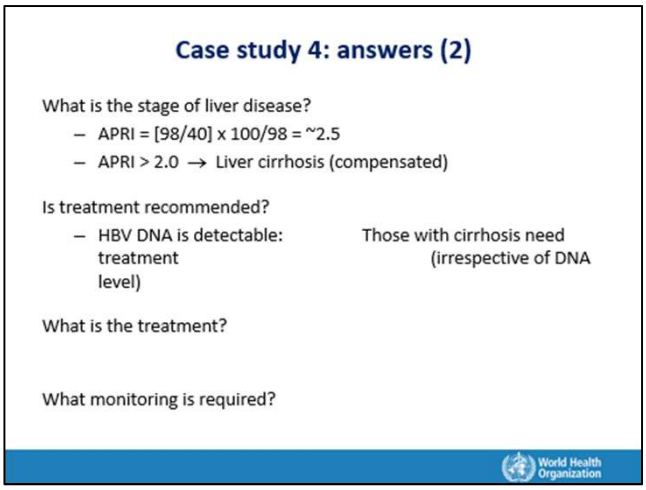
What is the treatment?

What monitoring is required?

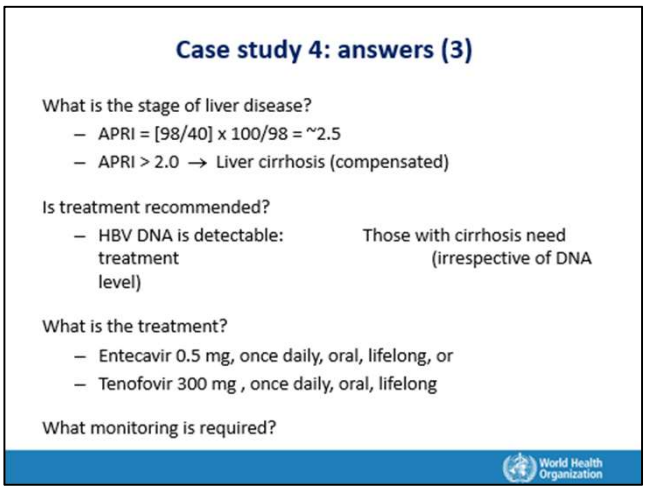
World Health Organization



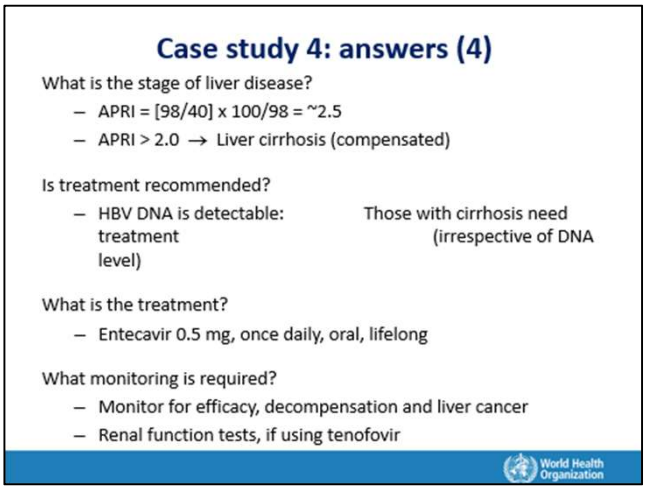
Because the APRI is more than 2, hence the patient has cirrhosis.



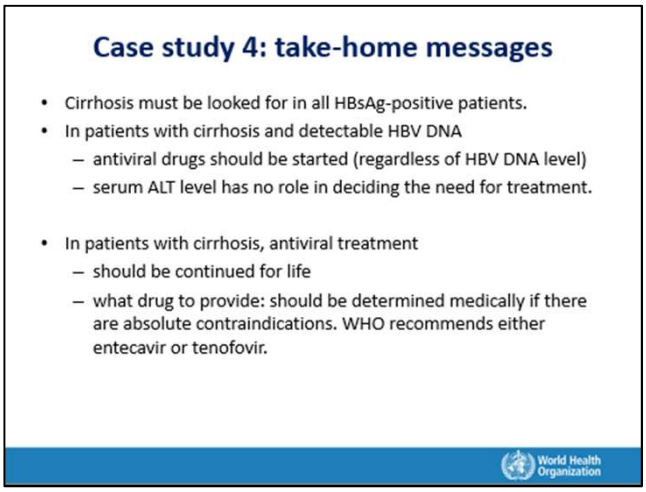
A patient with cirrhosis and raised HBV DNA needs antiviral drugs, hence we need to start antiviral drugs.



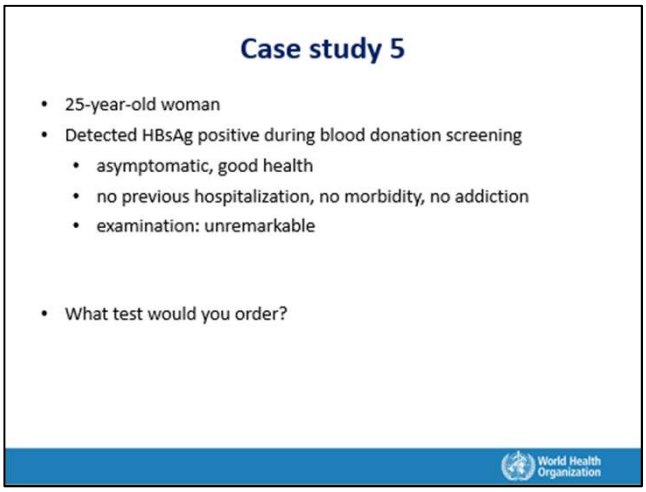
For compensated cirrhosis, we have two options – entecavir 0.5 mg or tenofovir 300 mg daily.



We need repeated evaluation during follow up for development of decompensation and HCC.



All HBsAg-positive patients should be evaluated for the presence of cirrhosis. All those with cirrhosis and detectable HBV DNA need antiviral drugs for life. All those with cirrhosis need follow up for progression to decompensation and HCC.



This is one of the most common scenarios that we come across. A 25-year-old lady donated blood and a got phone call from the blood bank after a few days stating that she was found to be HBsAg positive. Otherwise she does not have any symptoms. How would you proceed in this case?

Case study 5: test results

Investigations	Values
Haemoglobin (g/dL)	12.8
Platelets (x 10^9/L)	218
Total bilirubin (mg/dL)	0.8
Albumin (g/dL)	4.0
ALT (IU/L) AST (IU/L)	34 (<40 IU/L) 28 (<40 IU/L)
Prothrombin time (INR)	1.1
HBV DNA (copies/mL)	8000
USG abdomen	Normal liver size and echotexture Portal vein diameter = 10 mm Normal spleen; no ascites

World Health Organization

Her laboratory evaluation revealed normal liver enzymes and USG abdomen. HBV DNA is 8000 copies/mL.

How to interpret these laboratory data and proceed?

Case study 5: questions

What is the stage of liver disease?

Is treatment recommended?

What is the treatment?

What monitoring is required?

World Health Organization

We again have to answer the same questions.

Case study 5: answers (1)

What is the stage of liver disease?

- APRI = [28/30] x 100/218 = ~0.4
- APRI <2.0 → No cirrhosis

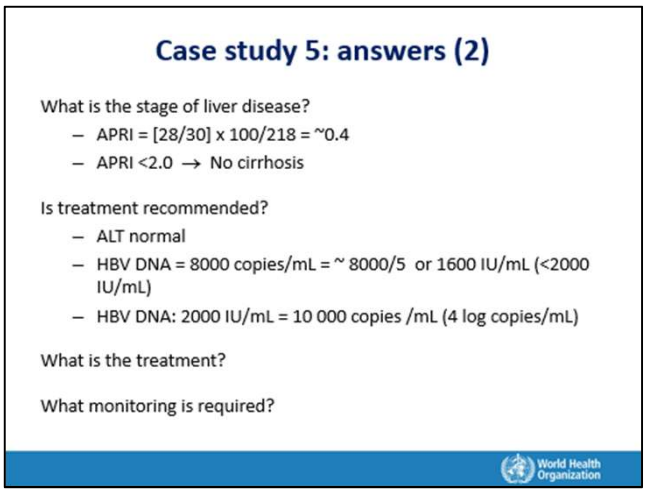
Is treatment recommended?

What is the treatment?

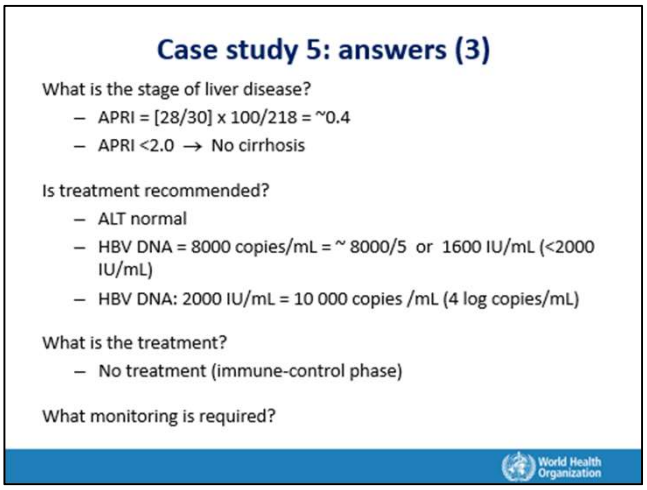
What is the monitoring required?

World Health Organization

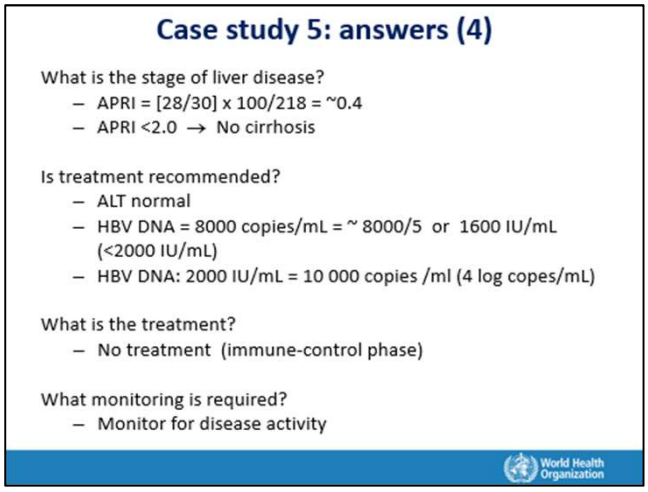
APRI is 0.4 hence she does not have cirrhosis.



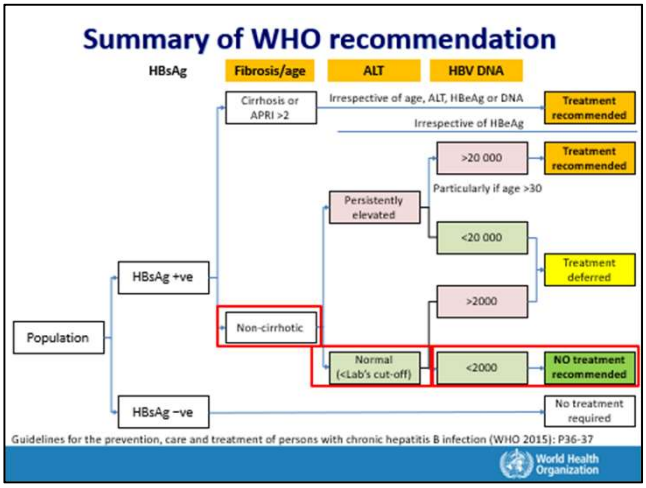
Her HBV DNA Is 8000 copies/mL. All the guidelines consider DNA in IU/mL but not in copies. DNA in copies can be converted to IU/mL by dividing the number of copies by five. Hence, the HBV DNA is relatively low.



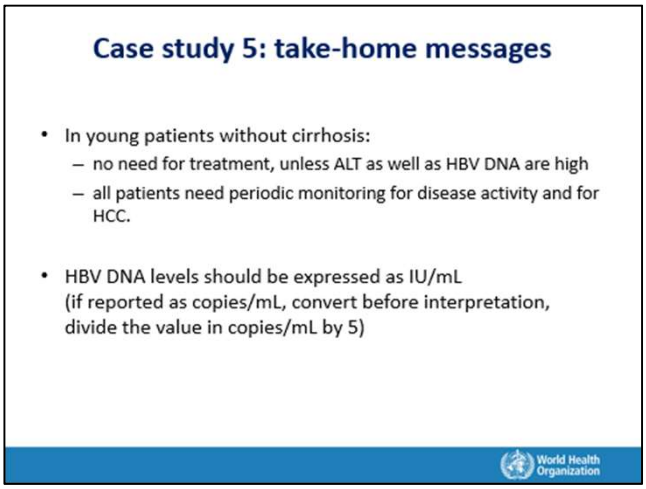
In view of the fact that there is no cirrhosis, the ALT is normal and DNA is low, antiviral treatment is not required.



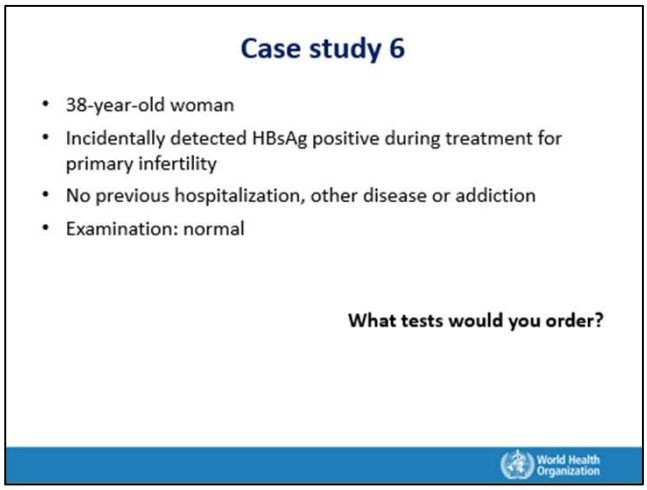
We need to re-evaluate very 6–12 months for disease activity.



In this flowchart, we can see the status of our present patient who does not require treatment as she has no cirrhosis, a normal ALT and low DNA.



In summary, patients with no cirrhosis, normal ALT and low DNA do not need treatment but need monitoring.



Again, we have an incidental detection of HBsAg in a women who was investigated for primary infertility.

Case study 6: test results

Investigations	Values
Haemoglobin (g/dL)	10.8
Platelets (x 10^9/L)	255
Total bilirubin (mg/dL)	1.2
Albumin (g/dL)	3.8
ALT (IU/L) AST (IU/L)	76 (<40 IU/L) 56 (<40 IU/L)
Prothrombin time (INR)	1.2
HBV DNA (IU/ml)	123,000
USG abdomen	Normal liver size and echotexture Portal vein diameter = 10 mm Normal spleen; no ascites

World Health Organization

Investigation revealed elevated liver enzymes and high DNA without any evidence of cirrhosis on USG abdomen.

Case study 6: questions

What is the stage of liver disease?

Is treatment recommended?

What is the treatment?

What monitoring is required?

World Health Organization

We have to proceed in a similar manner as we did previously.

Case study 6: answers (1)

What is the stage of liver disease?

- APRI = [56/40] x 100/255 = ~0.6
- APRI <0.6 → No cirrhosis

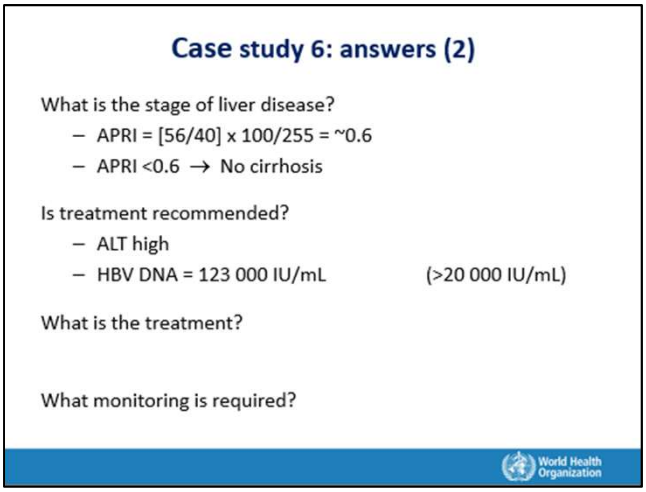
Is treatment recommended?

What is the treatment?

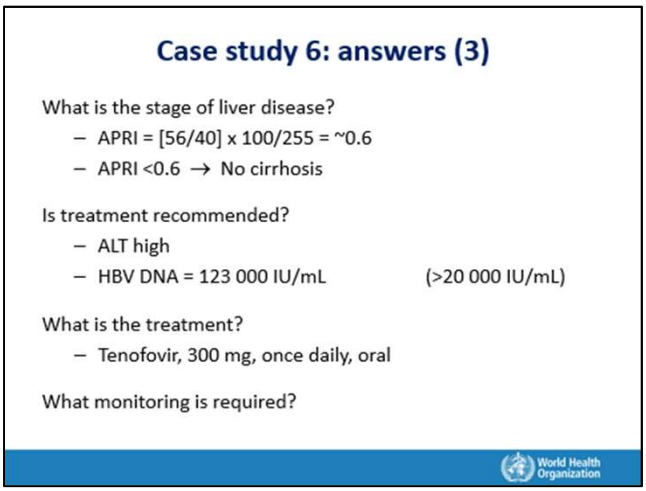
What monitoring is required?

World Health Organization

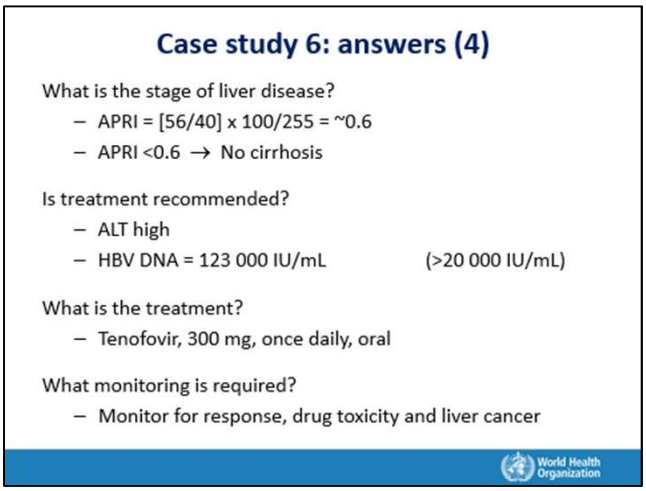
APRI of 0.6 indicates there is no cirrhosis.



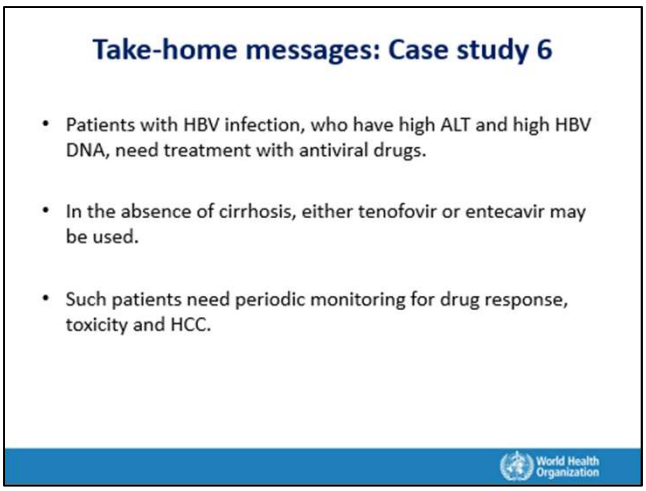
ALT and DNA are both high. Hence, antiviral treatment is indicated.



Tenofovir is the preferred antiviral in those without cirrhosis.



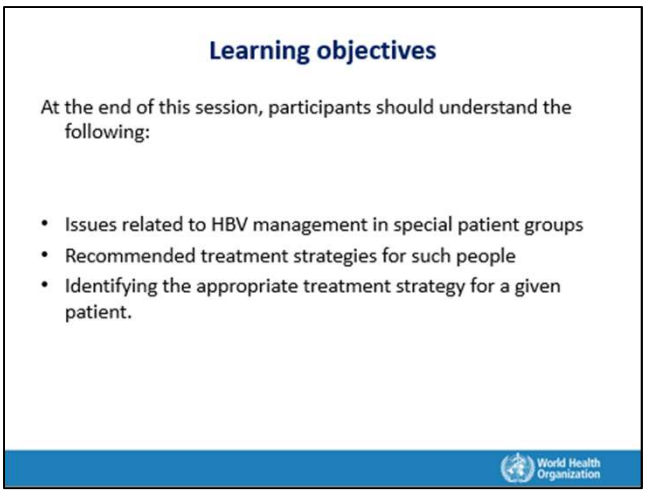
The patient will require monitoring and repeated evaluation for virus control, drug toxicity and HCC.



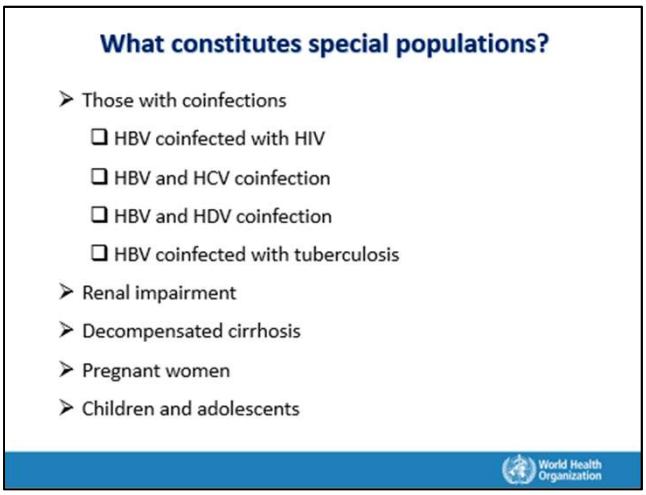
AN HBsAg-positive person with high ALT and DNA levels needs antiviral drugs. In the absence of cirrhosis, tenofovir is preferred over entecavir.

Module 12

Treatment of hepatitis B virus infection in special groups

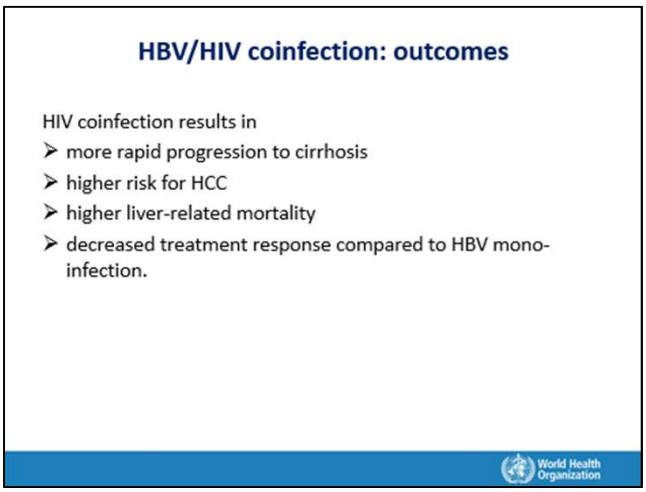


At the end of this session, we shall be able to approach and manage HBV infection in a few of the special population groups that we encounter most commonly.

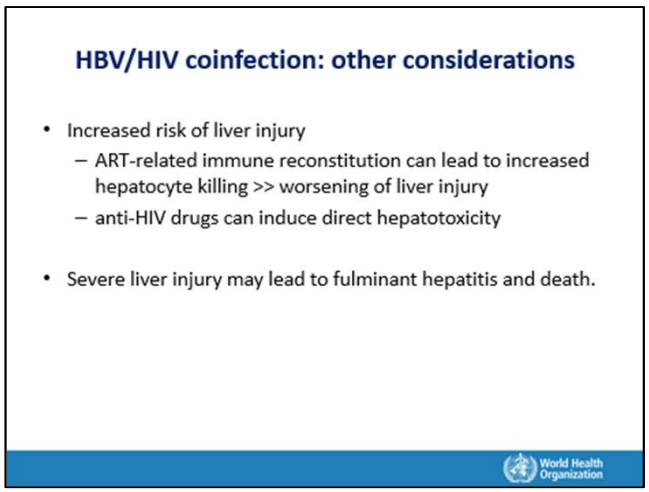


These are the groups of HBV-infected people who need special consideration in evaluation, management and follow up.

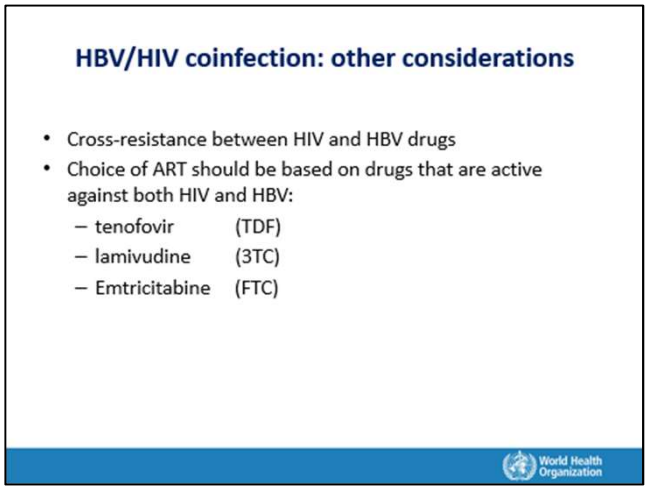
We will be discussing a few of them that could be managed at peripheral health-care facilities.



5–15% of HIV-infected persons are coinfected with HBV.
HIV coinfection adversely affects the clinical course of HBV infection.



Further, a coinfected person is also at risk of drug-induced liver injury because of antiretroviral drugs. Hence, a coinfeted person needs closer monitoring for toxicities, response and complications than a monoinfected person.

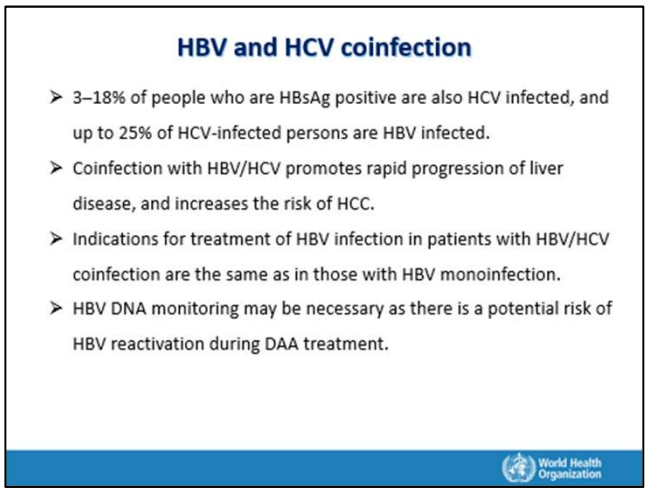


There is cross-resistance between HIV and HBV drugs.

HIV/HBV-coinfected persons should be simultaneously treated for both HIV and HBV infection. Choice of ART should be based on drugs that are active against both HIV and HBV.

We prefer to use tenofovir, (TDF) lamivudine (3TC) and emtricitabine (FTC) in the ART regimen.

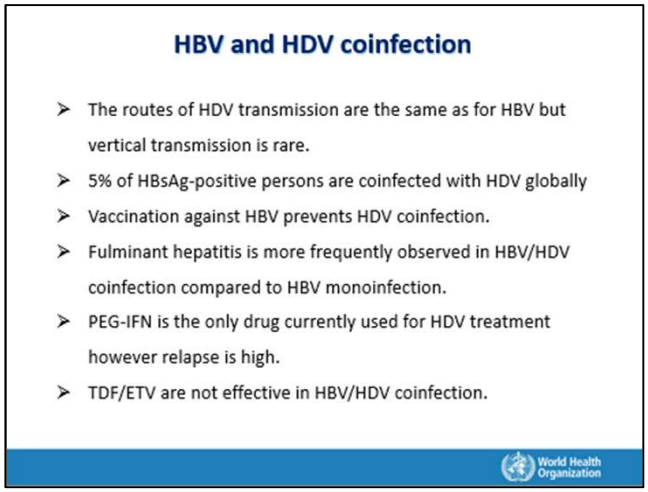
Entecavir is not recommended as first-line therapy because it can lead to resistance to HIV drugs.



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

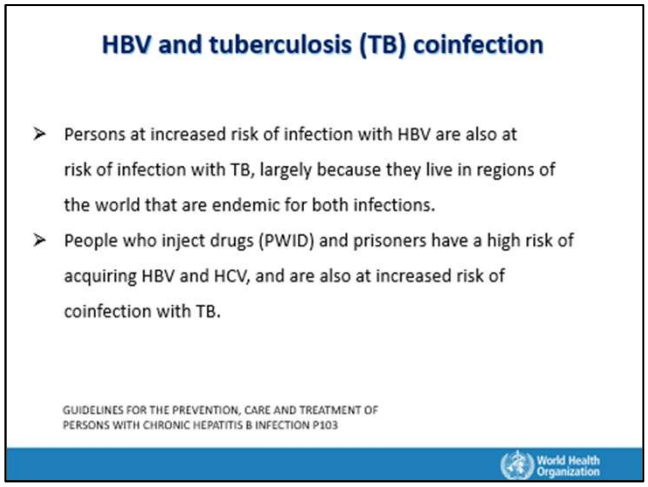
Both HBV and HCV are hepatotropic viruses and cause liver injury. Hence, their coinfection results in relatively rapid progression of liver disease and adverse outcomes.

HBV or HCV treatment indication, drug of choice, duration, etc. are similar to those in monoinfected persons.
In most coinfected 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.



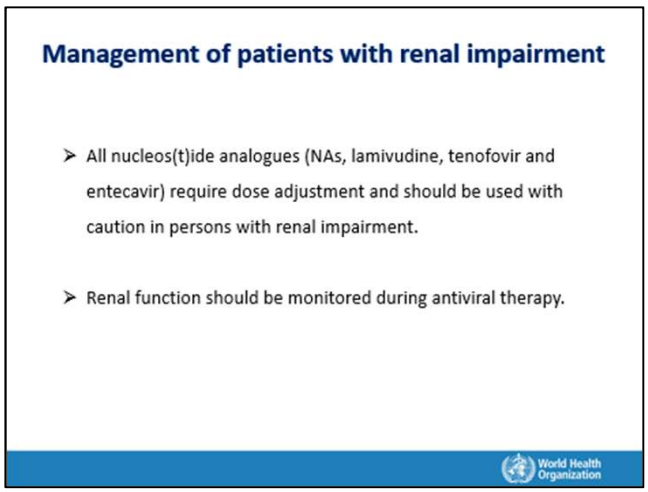
Hepatitis D virus (HDV) is an incomplete virus. HDV needs the presence of HBV surface antigen for its replication. Hence, HDV infection can occur only in an HBV-infected person. HDV infection can occur either in the form of superinfection (means HBsAg-positive person gets HDV infection) or coinfection (means HBV and HDV infect the person simultaneously). HBV/HDV coinfection may lead to acute liver failure. Around 5% of those with chronic HBV are also infected with HDV globally.

To date, pegylated interferon is the only drug used for HDV treatment, however relapse is high. Research for new drugs is in progress.



HBV and HCV infections are frequently encountered in patients with tuberculosis. This is primarily because all these diseases share the same endemic regions. We need to be cautious while starting antitubercular drugs in patients with HBV or HCV infection. We need to exclude cirrhosis carefully because such patients may develop hepatotoxicity and liver failure. In the presence of cirrhosis (regardless of its cause) modification of antitubercular drugs will be needed and more frequent monitoring for drug-induced liver injury.

In the presence of HBV or HCV infection, it is difficult to interpret the antitubercular treatment (ATT)-induced hepatotoxicity because of baseline LFT derangement secondary to HBV or HCV infection.



All those with chronic kidney disease (CKD) are at increased risk of acquiring HBV or HCV infection. HBV treatment in the presence of CKD, especially in those on dialysis, poses the problem of fibrosis assessment because the various measures of liver fibrosis are not reliable in those on dialysis.

Recommended dose reduction or dosing interval

Drug	Recommended dose reduction or dosing interval			
	CrCl (mL/min)[c]			
	≥50	30–49	10–29	<10, Haemodialysis or CAPD
Tenofovir [a,b]	One 300 mg tablet every 24 hours (7.5 scoops of powder every 24 hours)	One 300 mg tablet every 48 hours (or 160 mg [3 scoops] of powder every 24 hours)	One 300 mg tablet every 72–96 hours (or 60 mg [1.5 scoops] of powder every 24 hours)	Every 7 days or one 300 mg tablet following completion of approximately every 12 hours of dialysis (or 20 mg [0.5 scoops] of powder following completion of approximately every 12 hours of dialysis)
Entecavir	0.5 mg once daily[d]	0.25 mg once daily OR 0.5 mg every 48 hours	0.15 mg once daily OR 0.5 mg every 72 hours	0.05 mg once daily OR 0.5 mg every 7 days

PERSONS WITH CHRONIC HEPATITIS B INFECTION (WHO 2015)P76

World Health Organization

Tenofovir and entecavir, which are used for HBV treatment, need dose modification. Their doses are determined by the the glomerular filtration rate (GFR) of the patient.

Patients with decompensated cirrhosis

- All patients with decompensated cirrhosis should be considered for urgent antiviral therapy with tenofovir or entecavir, regardless of HBV DNA level.

World Health Organization

Decompensated liver disease is a very advanced stage of liver failure. Such patients have a very limited liver reserve. Any new, even trivial, injury may worsen the condition very fast. Hence, all those with decompensated cirrhosis should be treated with antivirals regardless of HBV DNA level. Antiviral drugs should be continued for life. In the presence of decompensated cirrhosis, entecavir is preferred to tenofovir because of toxicities (loss of bone mineral density and reduction in GFR).

HBV infection in pregnant women

- Mother-to-child HBV transmission must be prevented through a timely birth dose (<24 hours of birth) of HBV vaccine followed by two or three doses of the HBV vaccine.
- Indications for treatment in adults with chronic HBV infection also apply to pregnant women – for their own health. Tenofovir is the drug of choice
- Evidence is evolving globally and regionally on the use of tenofovir for prevention of mother-to-child transmission, particularly among pregnant women with a high HBV viral load, in addition to other interventions.to prevent MTCT of Hep B (new WHO guidelines forthcoming)

World Health Organization

Pregnant women with HBV infection need evaluation of their health as well as to prevent transmission of HBV to the fetus.

The most effective measure for prevention of mother-to-child transmission (PMTCT) are timely administration of the birth dose of hepatitis B vaccine followed by routine HBV vaccination.

Certain women with a high HBV DNA level may need treatment with tenofovir (new WHO global guidelines forthcoming in 2020)

Children and adolescents

- Children with HBV infection
  - are usually asymptomatic
  - are mostly in the immune-tolerant phase.
- Treatment is not considered in this phase due to
  - low curative response rates
  - concerns about long-term safety
  - risk of drug resistance (immunotolerant – very high viral load).
- Entecavir is approved for use in children above 2 years.
- Tenofovir is approved for use in children above 12 years.

World Health Organization

HBV infection is common among children. This high prevalence is partially contributed to by high rates of MTCT of HBV. In children, HBV infection is mostly asymptomatic and is in the immune-tolerant phase, which does not need treatment. When needed, we can use entecavir or tenofovir according to the age of the child.

Entecavir dosing in children

Group	Drug and dose
Children 2–12 years of age and weighing ≥10 Kg	Entecavir once daily as oral solution* (mL) if available
Body weight (Kg)	Dose (mL)* once daily
10–11	3
>11–14	4
>14–17	5
>17–20	6
>20–23	7
>23–26	8
>26–30	9
>30	10

*Solution containing 0.05 mg/mL (or 0.5 mg in 10 mL)

World Health Organization

The dose of entecavir will need modification according to the body weight of the child.

Persons who inject drugs (PWID)

- PWID who are actively injecting and sharing injecting equipment are at increased risk of infections such as HIV, hepatitis B and C.
- The priority interventions for HIV and hepatitis prevention among PWID remain harm reduction, in particular, needle and syringe programmes and opioid substitution therapy for those who are opioid-dependent.
- WHO recommends HBV vaccination of groups at highest risk of acquiring HBV infection, including PWID.

World Health Organization

The prevalence of HBV, HCV and HIV is high among the people who inject drugs. This is primarily because of needle-sharing and use of unsafe injection equipment.

These people need active screening and linkage with care for successful treatment. To avoid spread to others and reinfection, needle exchange programmes and opioid substitution therapy should be promoted.

All such persons who are HBsAg-negative should be vaccinated against HBV.

Module 13

Testing and serological markers for hepatitis C virus infection

Module 13

Learning objectives

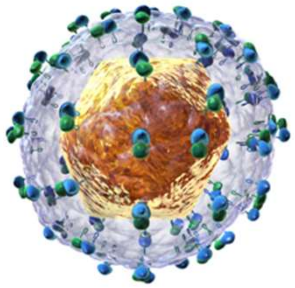
At the end of this session, participants would be able to understand the following:

- Various serological markers of HCV infection
- The significance and interpretation of these tests and their role in patient care
- Whom to test for HCV infection and how.

World Health Organization

In this session, we will learn the various serological markers used in the diagnosis and management of HCV. We will also learn about how to interpret these reports and draw a conclusion from them.

Hepatitis C virus

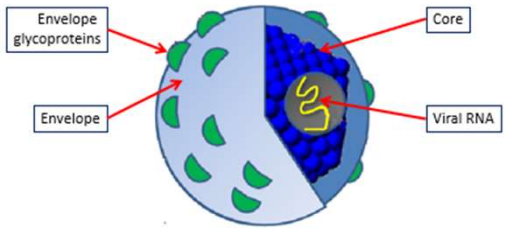


https://commons.wikimedia.org/wiki/File:HCV.png

World Health Organization

This is a picture of HCV.

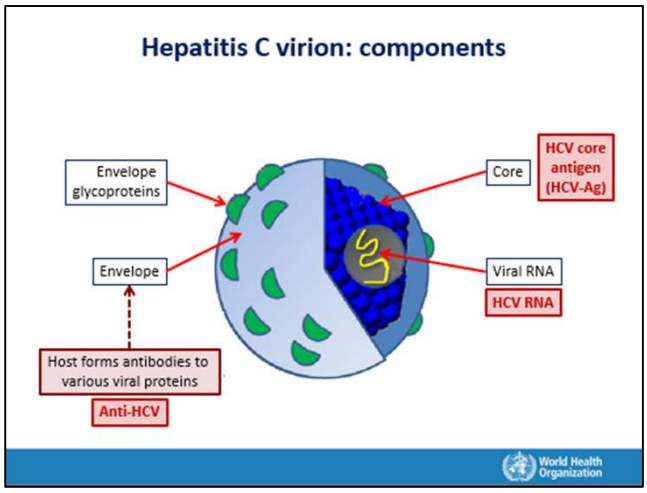
Hepatitis C virion: components



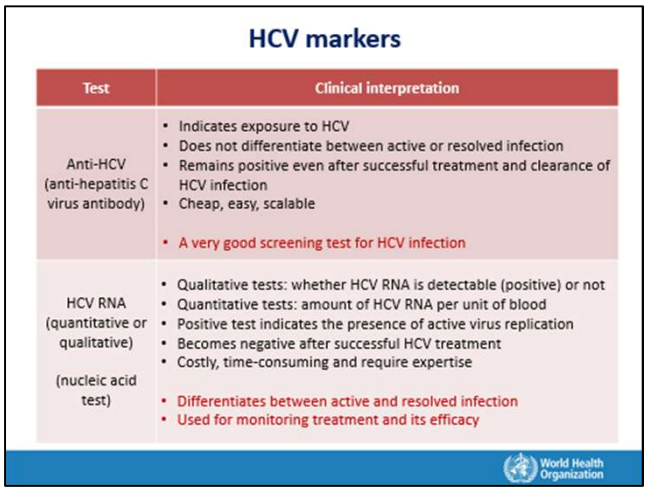
Adapted from: https://commons.wikimedia.org/wiki/File:HCV_structure.png

World Health Organization

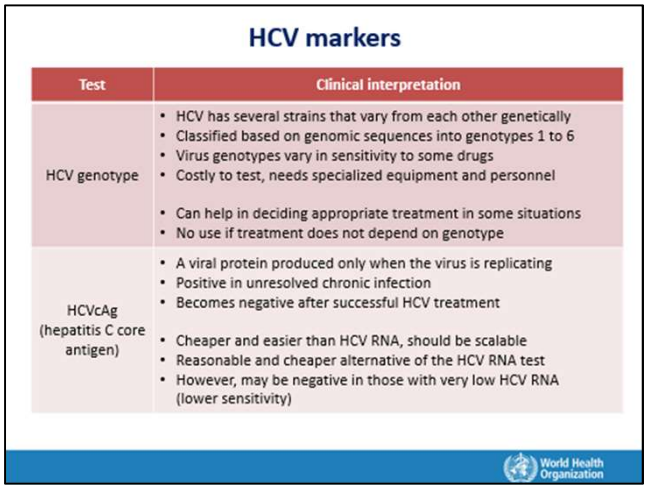
This is the schematic diagram of the hepatitis C virus. The virus has a "envelope" on the outermost aspect. This envelope contain surface glycoproteins, which induce host immunity for the development of antibodies. Inside the envelope, the virus has a protein core made up of core proteins. This protein core encloses the virus genome RNA.



The envelope protein induces host immunity for antibody formation (anti-HCV antibody). In the diagnosis and management of HCV, anti-HCV antibody, HCV core antigen and HCV RNA are used to determine the type of intervention



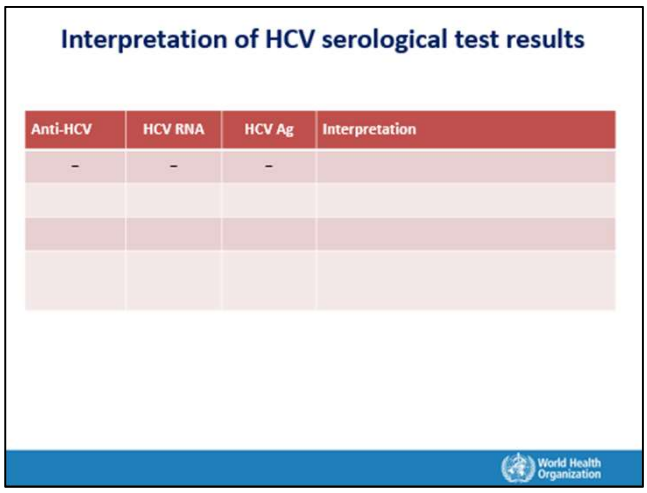
Anti-HCV antibody test indicates prior exposure to the virus but it does not differentiate between active or resolved HCV infection. Anti-HCV antibody does not have a protective effect. Anti-HCV antibody, after successful HCV treatment, persists for life but does not provide immunity against reinfection. It is the detectable HCV RNA, regardless of its quantitative value, which indicates active HCV infection. All those with detectable HCV RNA should be treated.



Hepatitis C virus has 7 major genotypes. The therapeutic response of these genotypes to different drugs varies. Earlier, it was common practice to test all those with detectable HCV RNA for the HCV genotype to select the appropriate treatment regimen. HCV genotype is a costly investigation that has limited availability; further, it needs time, facilities and expertise. In the present era, we have drugs that are equally effective against all the genotypes. These drugs are called pangenotypic drugs and they obviate the need for genotyping.

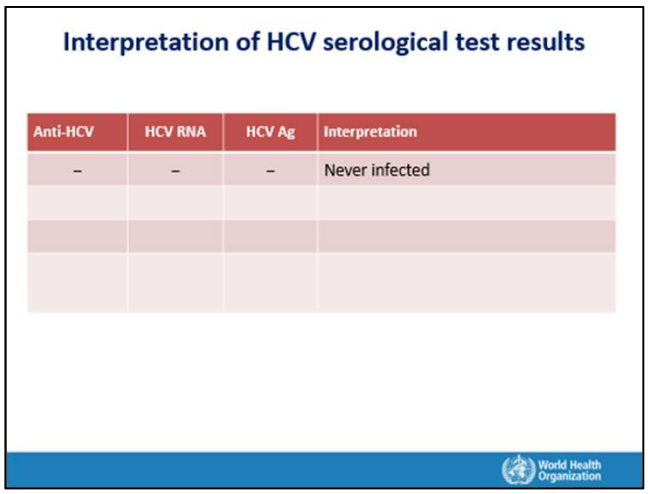
HCV core antigen (HCVcAg) is produced on replication of HCV. This antigen is released in the circulation and can be detected with simple tests. Recently, HCVcAg has emerged as an affordable and acceptable alternative to HCV RNA. HCVcAg testing, as compared to HCV RNA, has several advantages, such as lower cost, easy to test, less labour-intensive, and obviates the need for immediate testing after sample collection. HCVcAg can even be detected in dried blood spots.

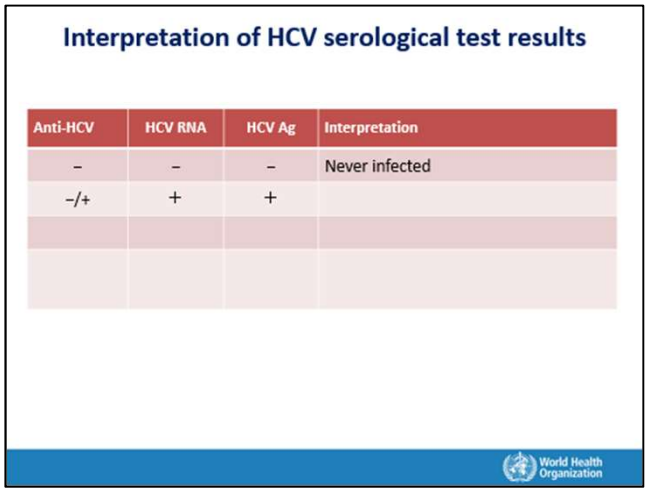
HCV antigen test gives the same information as HCV RNA. It has the potential to replace the RNA test – currently not widely accepted, but is likely to do so in future.



Let us recapitulate our understanding of HCV infection and interpretation of its diagnostic tests.

What is the condition shown here?





What about this scenario?

Interpretation of HCV serological test results

Anti-HCV	HCV RNA	HCV Ag	Interpretation
–	–	–	Never infected
–/+	+	+	Recent infection

World Health Organization

Interpretation of HCV serological test results

Anti-HCV	HCV RNA	HCV Ag	Interpretation
–	–	–	Never infected
–/+	+	+	Recent infection
+	+	+	

World Health Organization

Interpretation of HCV serological test results

Anti-HCV	HCV RNA	HCV Ag	Interpretation
–	–	–	Never infected
–/+	+	+	Recent infection
+	+	+	Persistent (chronic) infection

World Health Organization

Interpretation of HCV serological test results

Anti-HCV	HCV RNA	HCV Ag	Interpretation
–	–	–	Never infected
–/+	+	+	Recent infection
+	+	+	Persistent (chronic) infection
+	–	–	

World Health Organization

Interpretation of HCV serological test results

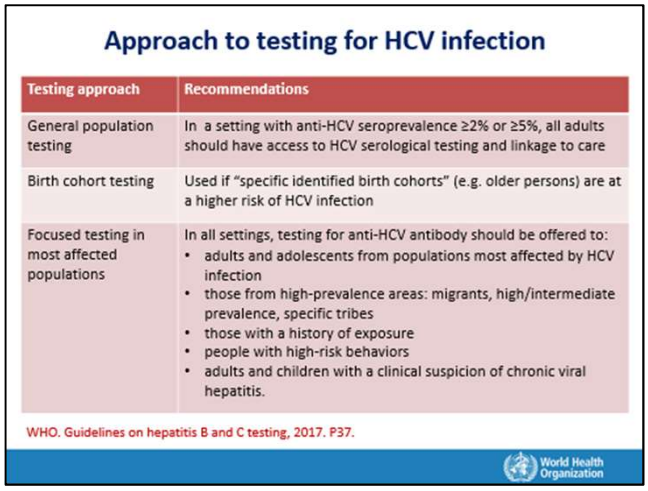
Anti-HCV	HCV RNA	HCV Ag	Interpretation
–	–	–	Never infected
–/+	+	+	Recent infection
+	+	+	Persistent (chronic) infection
+	–	–	Previously infected (infection resolved or cured)

World Health Organization

Approaches to detect HCV infection

- Mass screening
  (unselected testing of the general population)
- Targeted screening
  - Birth cohort testing
  - Specific high-risk groups
  - Blood donor screening (primarily done for blood safety)

World Health Organization



Approach to testing for HCV infection

Testing approach	Recommendations
General population testing	In a setting with anti-HCV seroprevalence ≥2% or ≥5%, all adults should have access to HCV serological testing and linkage to care
Birth cohort testing	Used if "specific identified birth cohorts" (e.g. older persons) are at a higher risk of HCV infection
Focused testing in most affected populations	In all settings, testing for anti-HCV antibody should be offered to: • adults and adolescents from populations most affected by HCV infection • those from high-prevalence areas: migrants, high/intermediate prevalence, specific tribes • those with a history of exposure • people with high-risk behaviors • adults and children with a clinical suspicion of chronic viral hepatitis.

WHO. Guidelines on hepatitis B and C testing, 2017. P37.

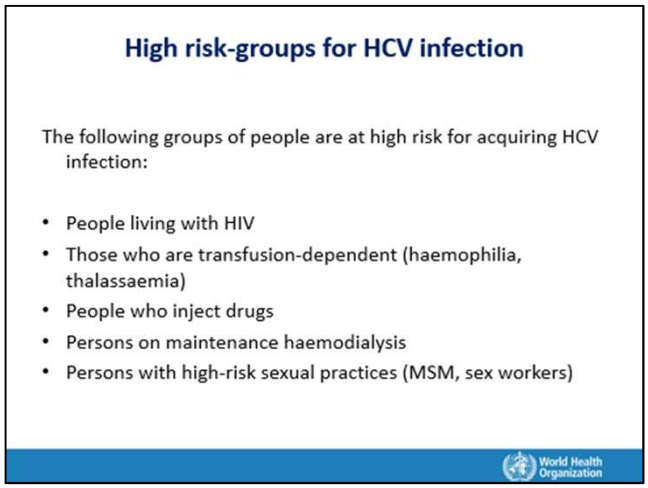
World Health Organization

In a setting of a public health programme, we can adopt any one of the following approaches. The approach selected is determined by several factors such as disease prevalence, cost of treatment in a given country, risk factors for HCV transmission in a given setting, etc.

First, we can consider screening all the population if the HCV prevalence in community is more than either 2% or 5%.

Second, we may restrict screening to high-risk groups only, which will increase the yield of the screening activity.

Third, we may focus on screening of people born in a certain specified period of time in the past; this approach is usually adopted when we know that most of the people were exposed to HCV during that specific period, such as people during World War II were exposed to HCV because of blood transfusion or promiscuity, etc.



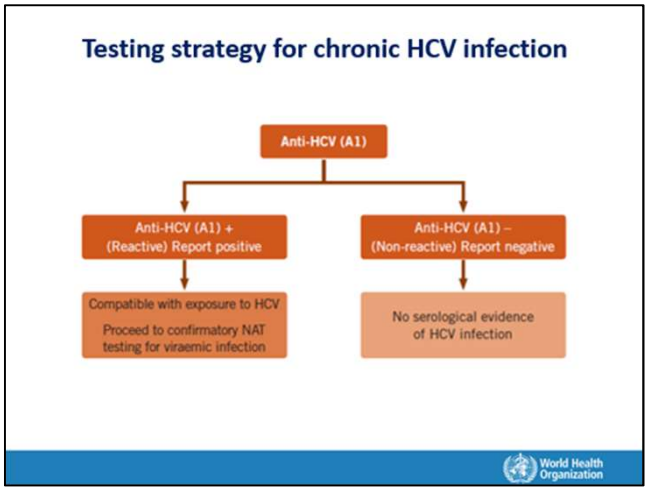
High risk-groups for HCV infection

The following groups of people are at high risk for acquiring HCV infection:

- People living with HIV
- Those who are transfusion-dependent (haemophilia, thalassaemia)
- People who inject drugs
- Persons on maintenance haemodialysis
- Persons with high-risk sexual practices (MSM, sex workers)

World Health Organization

These are the universally accepted groups of people who are at much higher risk for acquiring HCV infection than the general population.



Testing strategy for chronic HCV infection

World Health Organization

While screening a person for HCV infection, we need to use only a single anti-HCV antibody test kit. The kit used for screening should be WHO-prequalified to increase the sensitivity and specificity of the screening programme.

Summary

- A positive anti-HCV test indicates exposure to HCV, which is either active or has resolved.
- Anti-HCV remains positive following successful treatment.
- The anti-HCV antibody test can be used as a screening test for HCV infection, and has been employed in several different strategies.
- Tests for HCV RNA or HCVcAg serve as confirmatory tests. They indicate active infection and the need for treatment. These are also useful to monitor treatment and confirm cure.

World Health Organization

Module 14

Natural history of hepatitis C infection

Module 14

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.

World Health Organization

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

World Health Organization

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

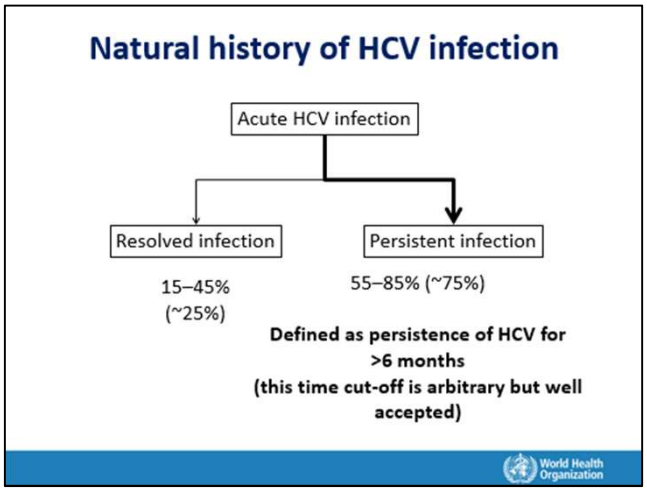
World Health Organization

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

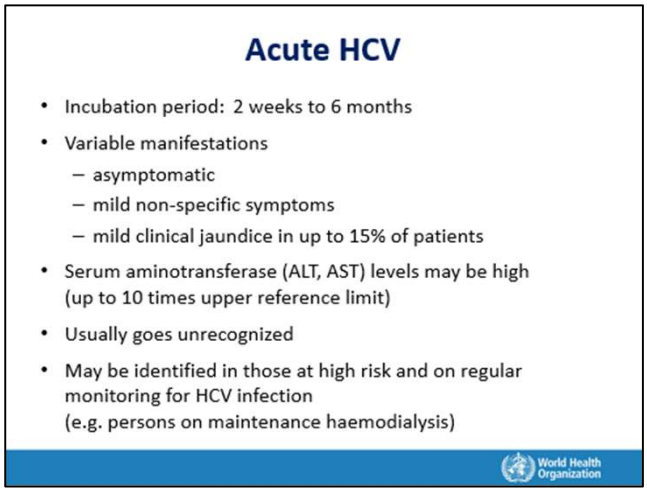
Transfusion of unsafe blood and unsafe injection practices are the most common sources of HCV transmission globally. In contrast to HBV and HIV, hepatitis C is infrequently transmitted from a pregnant woman to her baby in utero.

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.

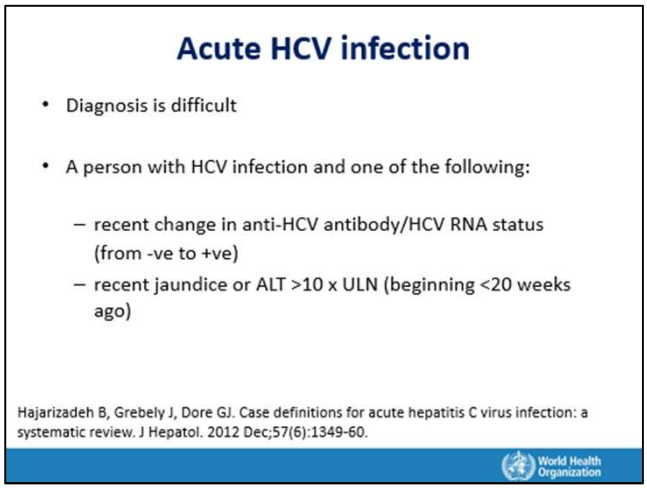
Further, sexual transmission of HCV, in particular among those who are in heterosexual monogamous relationships, is very infrequent.



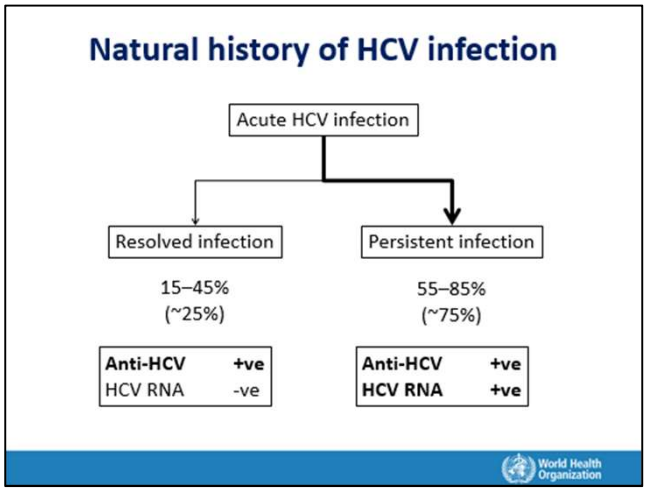
Following an infection with HCV, 15–45% (approximately one third) resolve and 55–85% (2/3rd) progress to chronic infection. Persistent infection is defined as persistence of HCV for >6 months. This time cut-off of 6 months is arbitrary and primarily taken as an analogy to chronic hepatitis B.



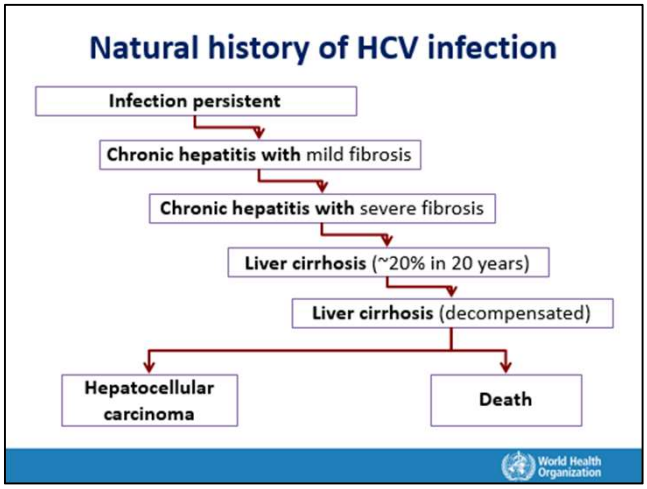
Following HCV exposure in a susceptible host, the virus causes acute HCV infection, which is mostly asymptomatic. The majority of patients with acute HCV are either asymptomatic or have non-specific systemic features such as low-grade fever, anorexia, etc. Clinical jaundice is very uncommon and hence 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.



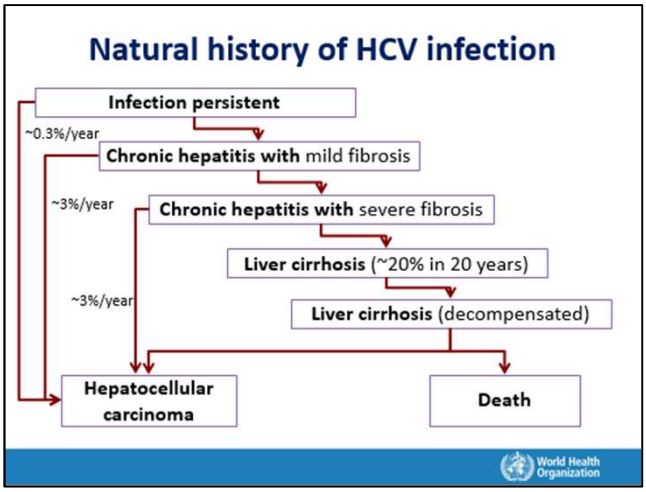
Empirically, acute HCV can be diagnosed in a person only if we find significant ALT elevation coupled with seroconversion from a negative anti-HCV test to a positive anti-HCV test.



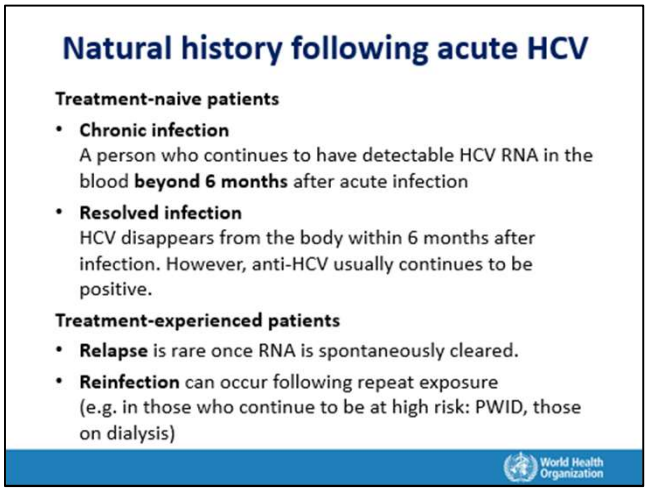
Usually, anti-HCV remains positive for life after the acute stage of the infection. It means that both resolved infection and persistent infection are anti-HCV positive. However, only patients with persistent infection remain HCV RNA positive (viraemia infection), Hence, we can distinguish persistent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



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.



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.



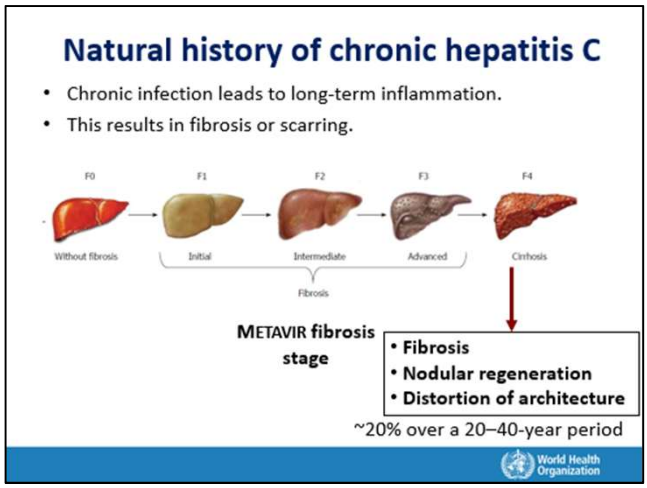
HCV infection is usually identified by the presence of anti-HCV antibody in the blood. It is important to realize that the presence of anti-HCV antibody does not indicate active infection because after natural clearance or successful treatment of HCV infection, the antibody continues to remain positive throughout life.

In a treatment-naive 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.

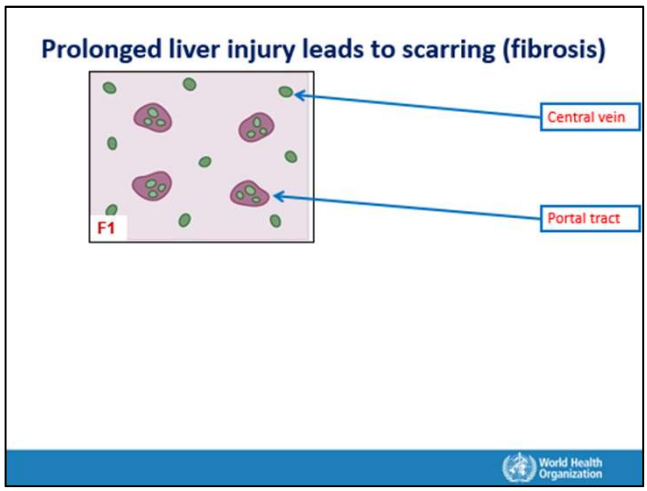
If the virus reappears within 12 weeks of stopping treatment, it should be considered as relapse but if the virus reappears after 12 weeks, then it indicates reinfection.

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.

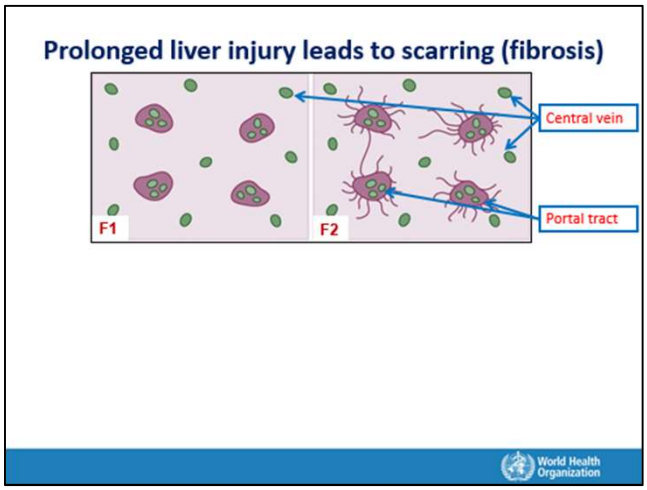


Chronic infection leads to long-term inflammation. It results in fibrosis or scarring. The METAVIR score is a tool used to evaluate the severity of fibrosis seen on a liver biopsy sample from a person who has hepatitis C. The grade indicates the amount of inflammation in the liver and the stage represents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

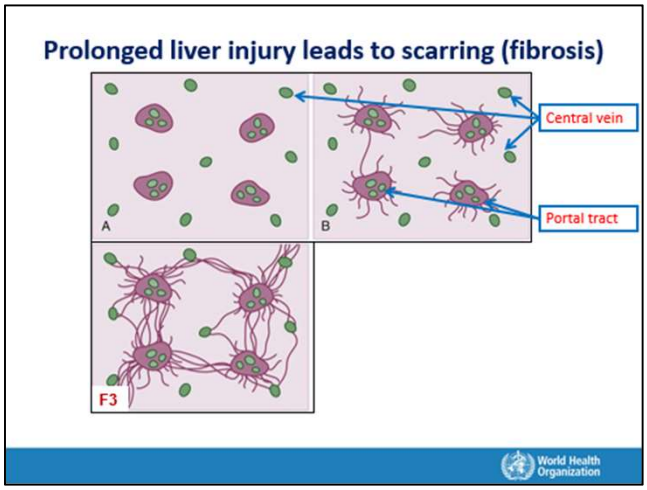
The rate is less than 20% in a 20–40-year period.



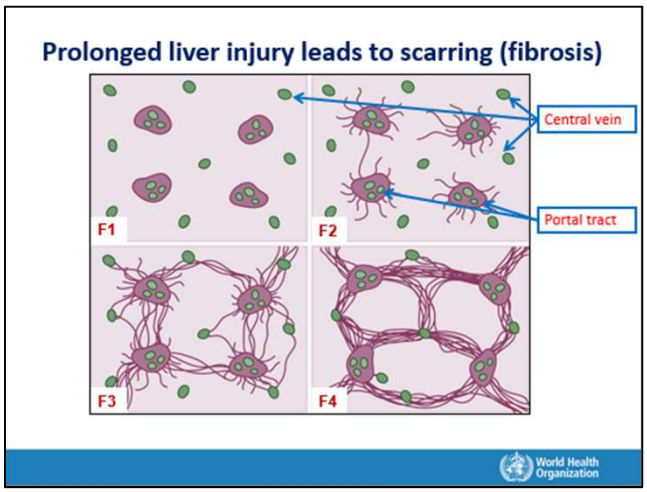
A fibrosis score of F1 (portal fibrosis without septa) means that the portal tracts are showing expansion because of fibrosis but fibrosis has not expanded into the hepatic lobule.



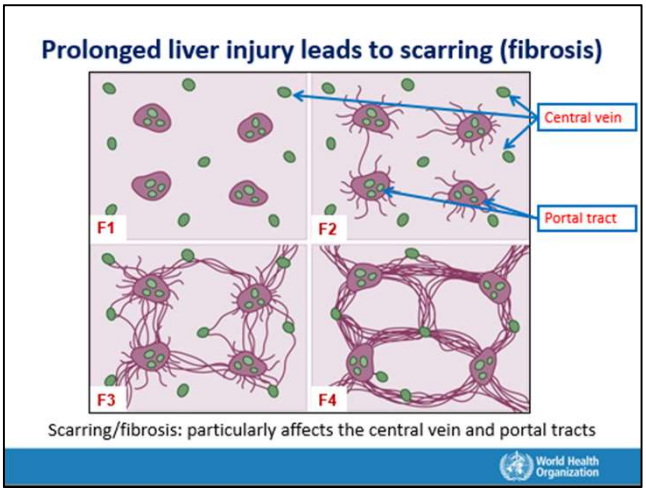
A fibrosis score of F2 (portal fibrosis with few septae) means the fibrosis has started expanding into the hepatic lobules beyond the portal tract, though the lobular fibrosis is limited. Such lobular fibrous septae are few in number, thin, and run from one to another portal tract. At this stage of fibrosis,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



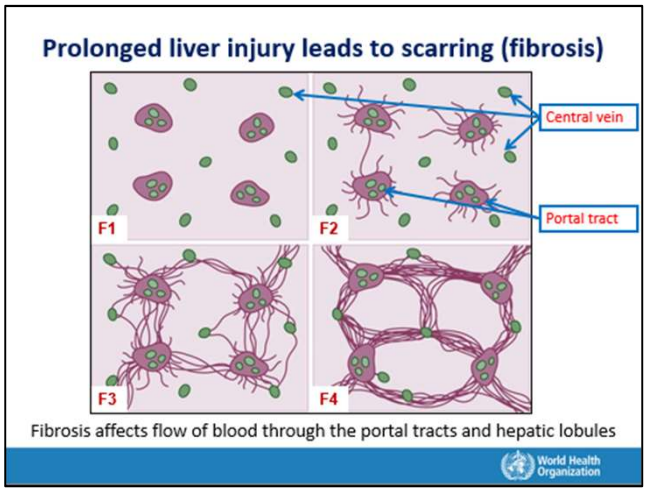
A fibrosis score of F3 (numerous septae without cirrhosis): means that fibrosis has extended well into the hepatic lobular parenchyma. The parenchymal fibrous septae are numerous, thicker and predominantly run between the adjacent portal tracts with a few thin septae running from the portal tracts to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



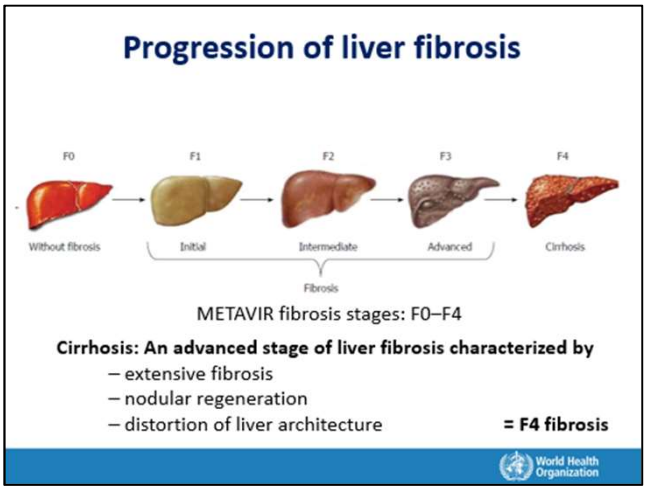
A fibrosis score of F4 (cirrhosis) means that there is histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury. In this stage, numerous thick septae connect either the portal tracts to the adjacent portal tracts or portal tracts to the central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



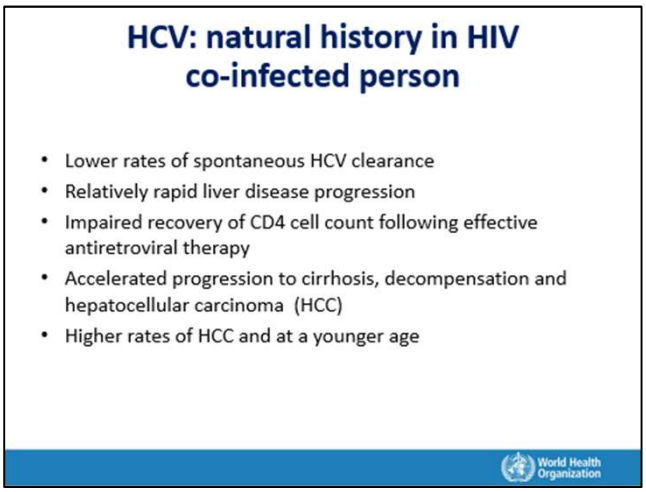
In the presence of numerous thick fibrous septae, the entire liver parenchyma is replaced by numerous small nodules of parenchymal cells, which are surrounded by thick fibrous bands.



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.



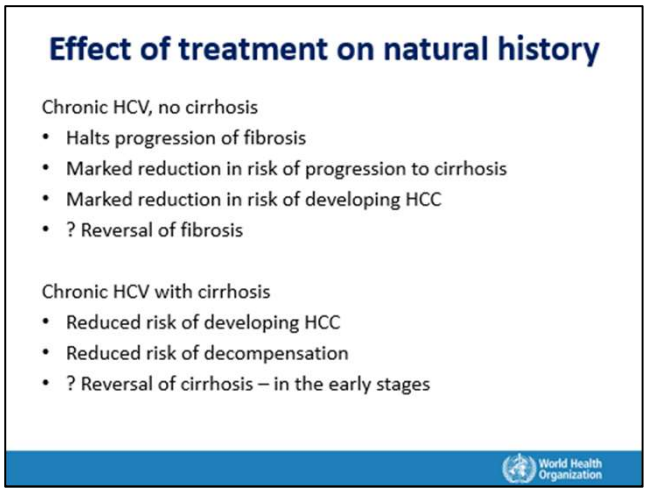
Cirrhosis is an advanced or terminal stage of liver fibrosis characterized by extensive fibrosis, nodular regeneration, and distortion of liver architecture.



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 in 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.

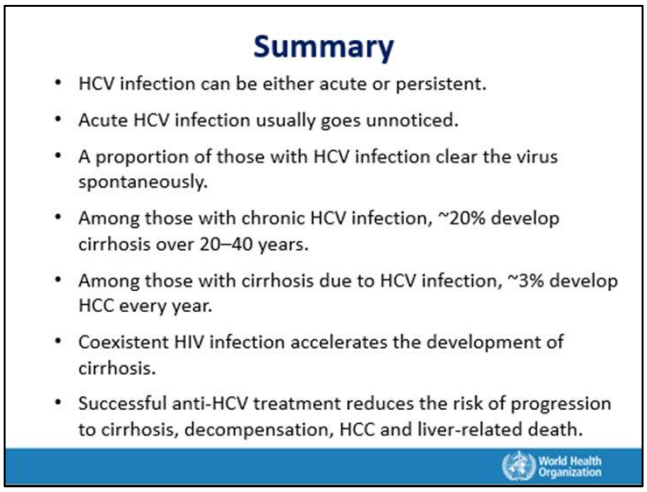
Hence, HIV/HCV-coinfected patients should be identified and be treated on apriority basis.



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.



The key messages of the presentation are:
• acute HCV is difficult do 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 accelerate 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.

Module 15

Clinical management of HCV infection (including case studies)

Module 15

Learning objectives

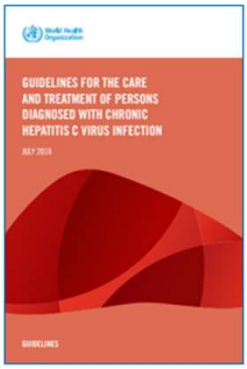
At the end of this session, participants would know the following:

- How to clinically assess HCV-infected persons
- Appropriate laboratory investigations needed for assessment
- Direct-acting antiviral drugs available for treating HCV infection
- Various treatment strategies recommended for HCV infection
- Identify the appropriate treatment strategy for individual patients with HCV infection.

World Health Organization

The objectives of this session are to provide participants with the knowledge needed for the assessment and interpretation of relevant laboratory investigations, and selection and execution of the appropriate treatment strategy for an HCV-infected person in a real-life scenario.

WHO Guidelines for HCV treatment



Latest guidelines:
Released July 2018

World Health Organization

This session is based on the HCV guidelines launched by WHO. The most recent WHO HCV guidelines were published at 2018.

Antibodies: what is it?

- Antibodies are part of immune response
- Specific antibodies are formed against a particular pathogen and may remain for life and be protective, example:
  - Measles is a viral disease which provides lifelong immunity
  - Anti-measles antibody remains positive for life
- In HCV, anti-HCV antibodies are form after HCV viral infection and remains in the serum even after clearance of the virus
- Detected through anti-HCV tests

World Health Organization

First – a recap on antibodies

As a part of the host's innate immune response, antibodies are formed in our body against any pathogenic invasion. Once a specific antibody is formed against a particular pathogen, it remains in the body for the rest of the host's life and protects them against a second attack by the same pathogen. A classic example is measles, which is a viral disease and the antibodies, developed either after natural infection or vaccination, protect the host for life. Hence, the presence of antibodies does not signify active infection but only indicates that there has been previous exposure.

Similarly, after HCV infection, anti-HCV antibodies are formed, which remain circulating in the serum after clearance of the virus. To identify an HCV-infected person, we are using an anti-HCV antibody test (but not an antigen test) to identify those who might still be having active HCV infection. This is in contrast to hepatitis B virus where we test a person for HBsAg (which is an antigen), which indicates ongoing active hepatitis B infection.

We must explain to patients about the perpetual persistence of anti-HCV even after successful treatment. This should be documented in his/her health records.

Acute versus chronic infection

	Acute	Chronic
Duration	<6 months	>6 months
Significance	A proportion of persons will clear the infection spontaneously (i.e. without any treatment)	Once chronic, most of the persons are unlikely to clear the infection
Need for treatment	Usually, no treatment is indicated	Treatment advisable

Laboratory tests do not permit this distinction
(except if a person was recently tested to be negative and has then become positive)

World Health Organization

The duration of acute infection is less than 6 months. A proportion of persons will clear the infection spontaneously (i.e. without any treatment). Usually, no treatment is indicated for acute hepatitis C. If the HCV infection continues for more than 6 months, it is labelled as chronic HCV infection. Once the infection becomes chronic, most persons are unlikely to clear the infection and hence treatment is advisable. However, laboratory tests do not help in distinguishing between acute and chronic HCV infection; except if a person was recently tested to be negative and has then become positive.

HCV infection: acute vs chronic

- HCV infection can be **suspected/assumed** to be acute if a person has had a possible exposure in the past 6 months
  - blood transfusion
  - unsafe injections
  - medical procedures, e.g. haemodialysis
  - surgery
  - sexual (rare).
- However,
  - a person with a recent risk factor may have pre-existing infection
  - no risk factor may be identified in many acute HCV cases.

World Health Organization

It is very difficult to identify acute HCV infection because HCV infection does not produce clinical jaundice or any other specific signs or symptoms. In the majority of cases, the diagnosis of acute HCV is based on assumptions. Most commonly, the diagnosis of acute HCV is suspected in people who were known to be anti-HCV negative and had exposure to a risk factor for HCV in the past six months and were recently found to be anti-HCV positive. These assumptions may not be accurate all the time.

Acute HCV infection

- Diagnosis 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.

World Health Organization

As of now, we do not have any universally accepted definition of acute HCV infection. In the literature, several definitions have been used for the diagnosis of acute HCV. Based on a systematic review of the available literature search, the most acceptable definition of acute HCV infection is given here: recent (within six months) change in anti-HCV antibody or HCV RNA serostatus (from negative to positive status) associated with clinical jaundice or ALT elevation of more than 10 times the normal.

HCV infection: active vs resolved

Definition

- Active = virus is still present in the host
- Resolved = no virus in the host
  (immune system has cleared the infection)

World Health Organization

If the virus is still circulating in the host blood then it is called active infection.

HCV infection: active vs resolved

Definition

- Active = virus is still present in the host
- Resolved = no virus in the host
  (immune system has cleared the infection)

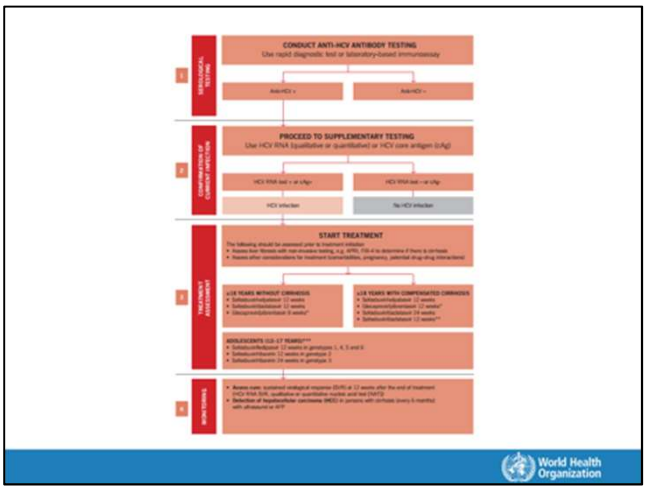
Laboratory diagnosis

- Active = serum HCV RNA +ve
- Resolved = serum HCV RNA –ve

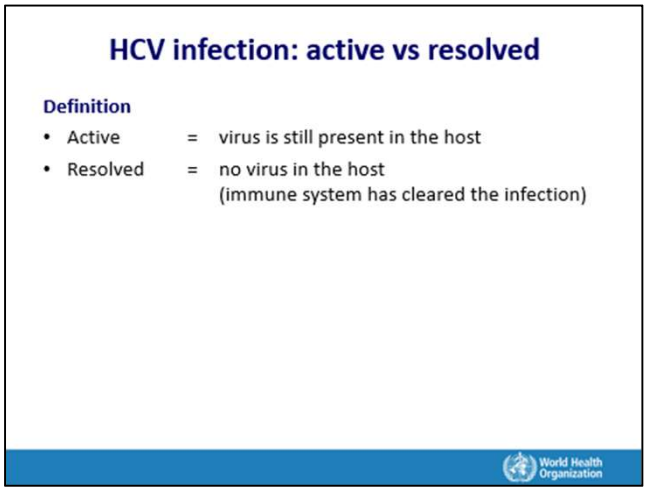
All persons with active HCV infection should be considered for treatment

World Health Organization

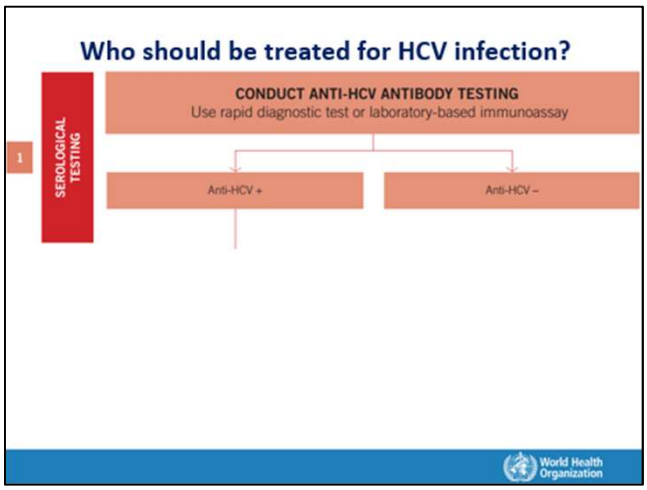
Active infection is diagnosed by the presence of HCV RNA in the serum and all those with active HCV infection, regardless of the level of viraemia, should be treated.



The slide shows a summary algorithm for the diagnosis, treatment and monitoring of chronic HCV infection.

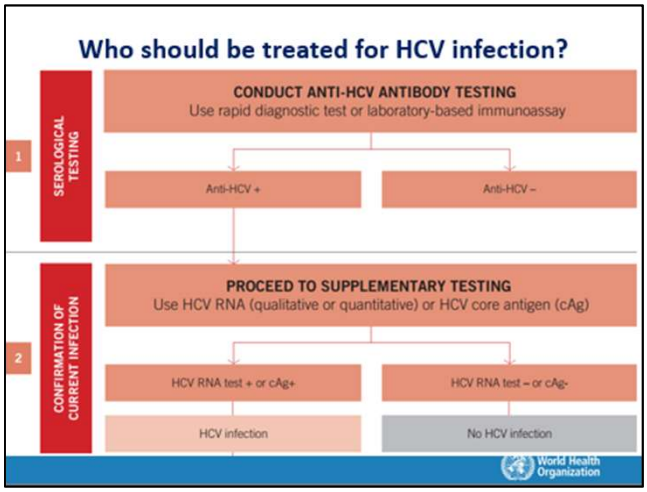


If the virus is still circulating in the host blood then it is called active infection.



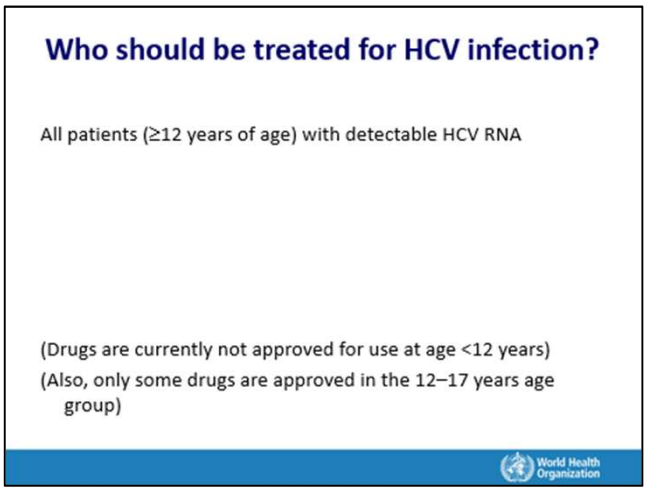
At the first stage, serological testing such as anti-HCV antibody testing should be conducted.

When it is positive, we should go to te next stage.

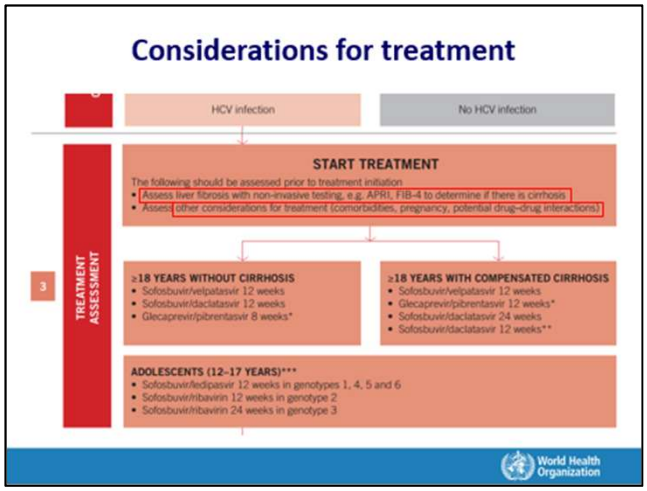


At the second stage, supplementary testing such as HCV RNA or cAg should be tested.

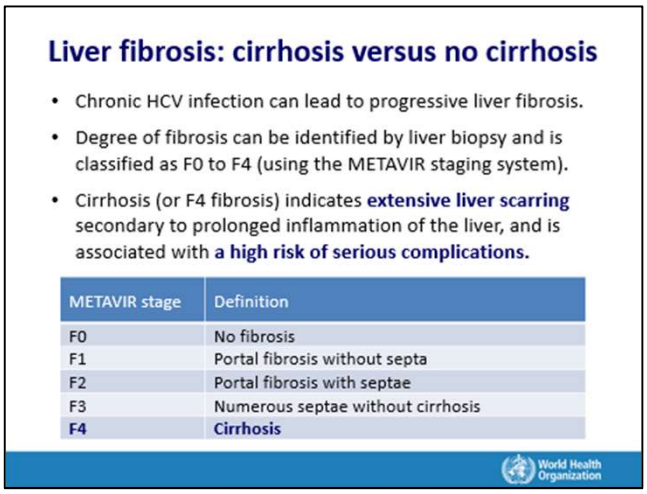
When it is positive, we can confirm current HCV infection.



At present, HCV treatment is permitted for patients aged 12 years or more because drugs are not approved for use in children below 12 years of age. They are likely to be approved soon (clinical trials ongoing for use of drugs among younger age groups).



In the third phase, we should conduct treatment assessment. Before treatment, we should assess for liver fibrosis with non-invasive testing such as APRI, FIB-4 to determine if there is cirrhosis and assess other considerations for treatment such as comorbidities, pregnancy and potential drug–drug interactions.



Chronic viral hepatitis induces liver fibrosis. The severity of liver fibrosis is a continuous process. For ease of understanding and communication, the severity of liver fibrosis is graded into five grades from no fibrosis (called F0) to cirrhosis (called F4).

From the HCV management and prognosis point of view, in every patient, the physician needs to determine whether the fibrosis has progressed to the stage of cirrhosis or not. Those with cirrhosis need a longer duration of treatment, addition of ribavirin, lower chance of response, higher risk for relapse, and lifelong monitoring and follow up (after successful antiviral treatment and virus eradication) for hepatocellular carcinoma.

Module 15

Diagnosis of cirrhosis

- Clinical features
- Indirect tests
  - haemogram, especially platelet count
  - biochemical tests: ALT, AST, albumin
  - **composite measures**
    - **FIB-4, APRI, Fibrotest**
- Imaging
  - **ultrasound**
- Specialized tests
  - endoscopy for varices
  - **liver stiffness (transient elastography)**

World Health Organization

The presence of cirrhosis can be identified with a combination of clinical findings (oedema, ascites, variceal bleed, hepatic encephalopathy), haemogram (which may show pancytopenia; the platelets are the first to show a reduction in number), liver function tests (low serum albumin and composite scores such as APRI, FIB-4), ultrasound abdomen (nodular and shrunken liver, dilated portal vein, splenomegaly, etc), and endoscopy (for oesophageal and gastric varices).

If available, liver stiffness measurement (transient elastography) could also help in diagnosing cirrhosis.

Cirrhosis versus no cirrhosis

	Components	Requirements	Cost
APRI	AST, platelets	Simple serum and haematology test	+
FIB-4	Age, AST, ALT, platelets		
FibroTest	GGT, haptoglobin, bilirubin, apoprotein A1, α2-macroglobulin	Specialized tests at designated laboratories	++
FibroScan ®	Transient elastography	Dedicated equipment	++ +

AST	aspartate aminotransferase
ALT	alanine aminotransferase
GGT	gamma glutamyl transpeptidase
APRI	aspartate aminotransferase-to-platelet ratio index
FIB-4	fibrosis-4 score

World Health Organization

There are a few composite scores that have been validated for the diagnosis of cirrhosis. The calculation of these scores requires a few simple laboratory parameters. The most commonly used scores are APRI, FIB-4, and FibroTest.
Among these composite scores, APRI (AST-to-platelets ratio index) is the one that is the most extensively studied, validated and used. The widespread acceptability of APRI is contributed by several of its qualities such as use of easily available parameters, ease of calculation without a calculator, and extensive validation in various populations across the grades of fibrosis.

These composite scores, other than APRI, have limitations such as the need for an uncommon laboratory variable, calculator or computer-based calculation or need of an specific instrument.

FibroScan is one of the newer devices that has been used for fibrosis assessment. This is an ultrasound-like machine that non-invasively measures liver fibrosis. Itis easy to use and can be repeated frequently. The major limitation of the FibroScan is its huge cost and need for a dedicated person to maintain the quality of fibrosis assessment.

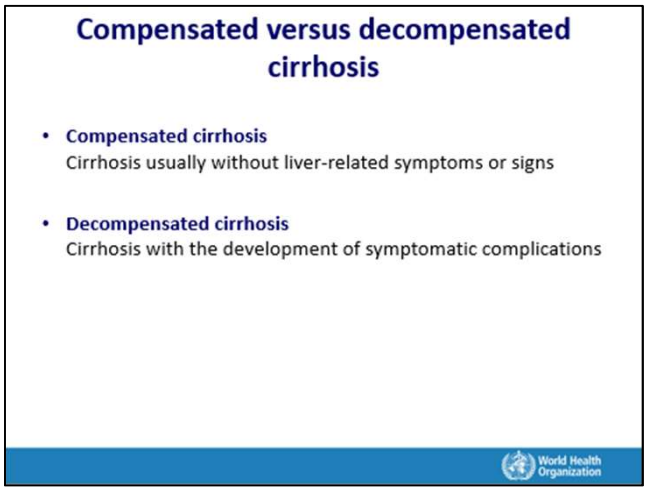
APRI: cirrhosis versus no cirrhosis

- In resource-constrained settings, two cut-off values help in treatment prioritization.
- Values above the high cut-off
  - high probability of cirrhosis
- Values below the lower cut-off
  - high certainty that there is no cirrhosis
- Between the two cut-offs
  - Cirrhosis possible but not very certain

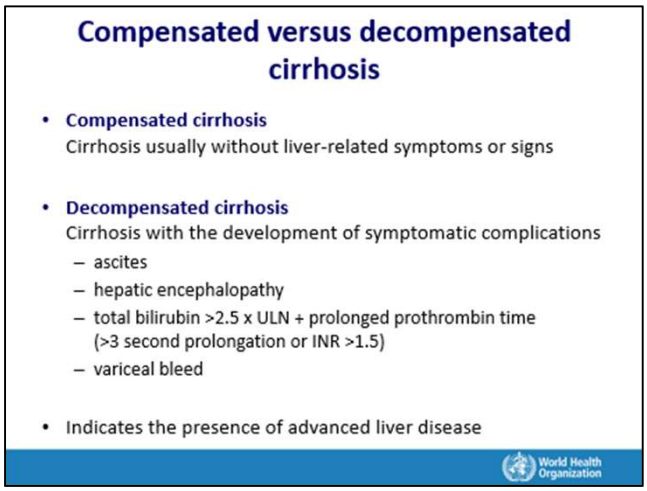
World Health Organization

APRI and FIB-4 are the two most commonly used composite measures of liver fibrosis. These two indices could easily be calculated with simple laboratory parameters. Hence, WHO has recommended their use for fibrosis assessment. APRI is the most widely used. These indices are useful in determining the presence or absence of liver cirrhosis. These indices have limited roles in differentiating between the various grades of fibrosis such as F1 versus F2 fibrosis. In the era of DAAs, for patient management and follow up, we need to know whether cirrhosis is absent or present but we do not need to know the grade of fibrosis if cirrhosis is absent.

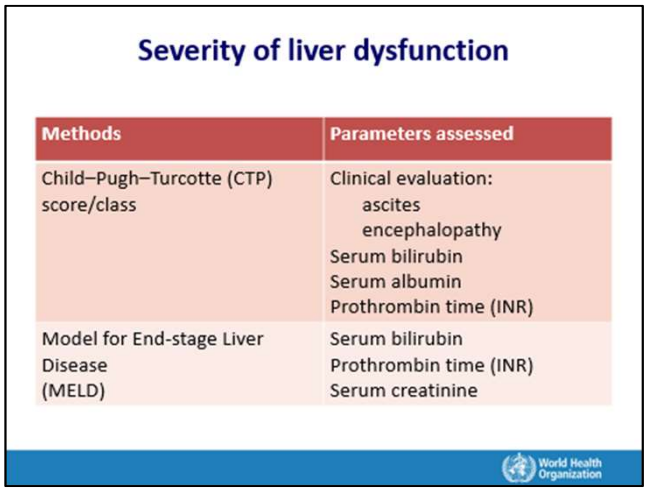
For each of these indices, WHO recommended two cut-off levels to define cirrhosis: (i) lower cut-off value which has a high sensitivity (means detects true positive) to detect cirrhosis if it is present and (ii) upper cut-off value, which is more specific for diagnosing cirrhosis. Values above the high cut-off indicate a high probability of having cirrhosis; any value below the low cut-off value indicates a very low probability of having cirrhosis. These two cut-offs may be used in resource-constrained countries where anti-HCV treatment is prioritized on the basis of severity of fibrosis; in such places, those with scores above the higher cut-off will receive treatment on a priority and those with a score below the lower cut-off will not be treated. Those with score between the low and high cut-off values could either be monitored at regular intervals for disease progression or could be treated if resources become available.



Another important step in the management of a cirrhosis patient is to decide whether the cirrhosis has progressed to the stage of decompensation or not.



Decompensation is defined by the presence of clinical symptoms due to cirrhosis or portal hypertension such as ascites, variceal bleed, hepatic encephalopathy and jaundice.



We can assess the severity of liver dysfunction by 2 methods:
First, the Child–Pugh–Turcotte (CTP) score assesses disease severity on the basis of parameters that are determined by clinical evaluation such as ascites and encephalopathy. Serum bilirubin, serum albumin, and prothrombin time (INR) should be estimated as well. Hence this score is a relatively subjective score.
Model for End-stage Liver Disease (MELD) assesses serum bilirubin, prothrombin time (INR) and serum creatinine.

Child–Pugh–Turcotte Score

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time Seconds prolonged or International normalized ratio	<4 <1.7	4-6 1.7-2.3	>6 >2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			

World Health Organization

In terms of the Child–Pugh–Turcotte Score, we can divide each clinical and laboratory parameter criteria into three grades. As a result, the CTP score ranges between 5 and 15. Class A is 5 to 6 points, class B is from 7 to 9 points, and class C is from 10 to 15 points.

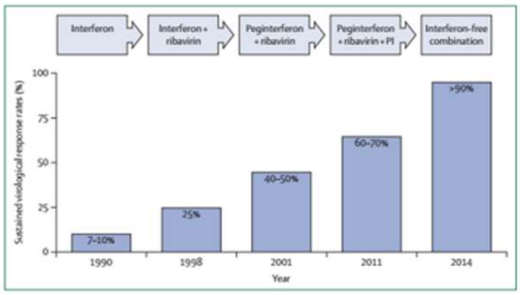
Why treat HCV infection?

- Delay the progression of cirrhosis
- Reduce the incidence of hepatocellular carcinoma
- Improve the quality of life
- Improve long-term survival (reduce death)
- Potentially, reduce transmission

World Health Organization

As of now, every person with active HCV infection should be treated because successful HCV treatment confers several advantages on the host such as delay in the progression of fibrosis, reduced risk for HCC, improvement in the quality of life and survival. Successful HCV treatment may even cause regression of the liver fibrosis. Because person-to-person HCV transmission is relatively uncommon, hence HCV treatment plays a limited role in preventing HCV transmission.

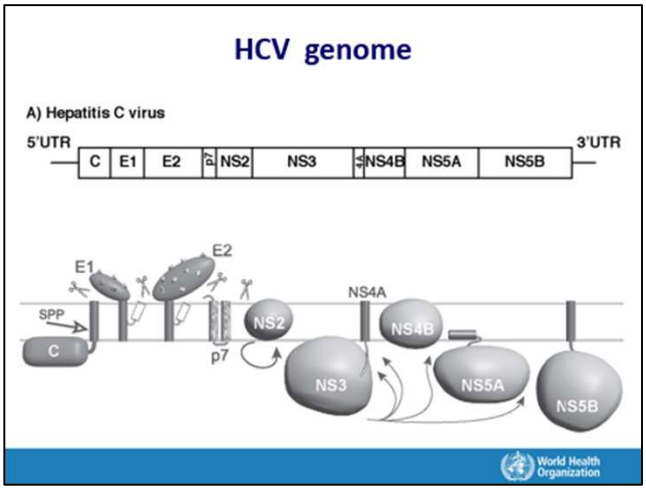
Evolution of HCV treatment over time



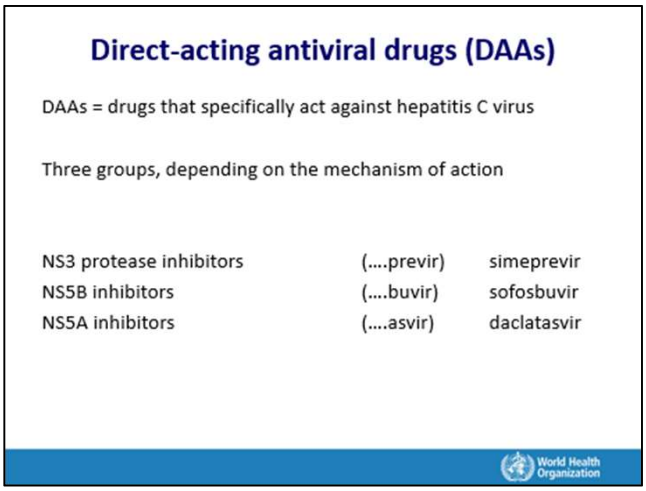
World Health Organization

This slide shows the evolution of HCV treatment over time. In the 1990s, interferon and ribavirin were the only medications to treat HCV. The sustained virological response (SVR) rate was only 7–25%. In the 2000s, pegylated interferon was available, therefore, the SVR rate increased to 40–50%. In the beginning of the 2010s, protease inhibitors were developed and became available. The SVR rate was 60–70%. Interferon-free combinations were innovative and greatly increased the SVR rate to over 90%.

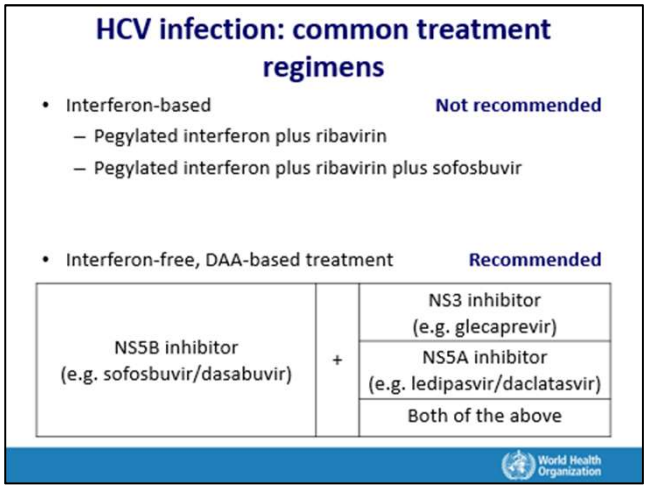
Module 15



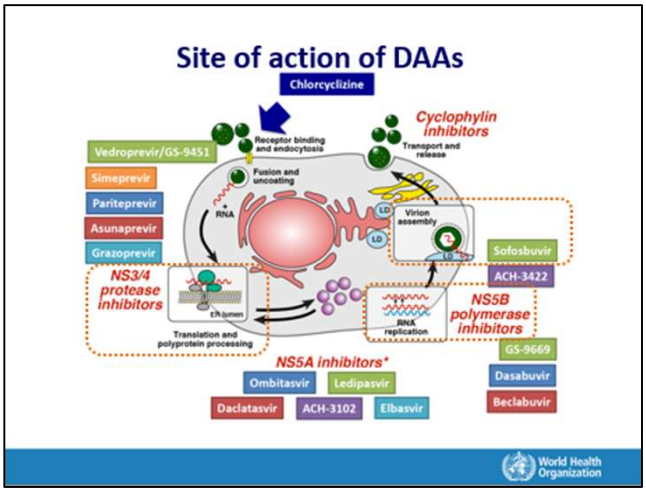
Hepatitis C virus has a positive-sense single-stranded RNA genome. The genome consists of a single open reading frame that is about 10 000 nucleotide bases long. This single open reading frame is translated to produce a single protein product, which is then further processed to produce smaller active proteins. This is why on publicly available databases, such as that of the European Bioinformatic Institute, the viral proteome consists of only 2 proteins. At the 5' and 3' ends of the RNA are the untranslated regions (UTRs), which are not translated into proteins but are important for translation and replication of the viral RNA. The 5' UTR has a ribosome binding site or internal ribosome entry site that initiates the translation of a very long protein containing about 3,000 amino acids. The core domain of the HCV internal ribosome entry site (IRES) contains a four-way helical junction that is integrated within a predicted pseudoknot. The conformation of this core domain constrains the open reading frame's orientation for positioning on the 40S ribosomal subunit. The large pre-protein is later cleaved by cellular and viral proteases into 10 smaller proteins that allow viral replication within the host cell, or assemble into mature viral particles. Structural proteins made by the hepatitis C virus include core protein, E1 and E2; nonstructural proteins include NS2, NS3, NS4A, NS4B, NS5A and NS5B.



All the oral anti-HCV drugs, which are called DAAs and are used today, can be categorized into three groups. Each of these drugs inhibits a specific non-structured protein of the virus. The names of these drugs are difficult to remember and hence their names are provided with specific suffixes such as previr, buvir and asvir at the end of their names.



Till a couple of years ago, HCV infection was treated with pegylated interferon but now pegylated interferon is not used for HCV treatment. Among the currently available oral drugs, NS5B inhibitors, mainly sofosbuvir, forms the backbone and is used in combination with drugs from one or both remaining groups of DAAs.

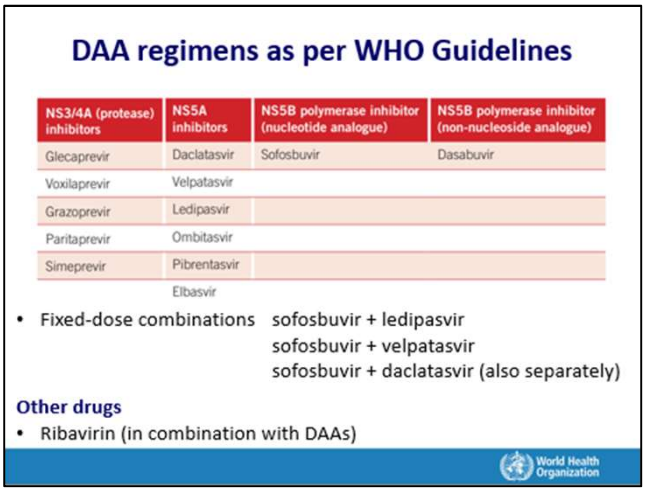


There are 4 targets on the hepatitis C virus that DAA medications attack to destroy the virus.

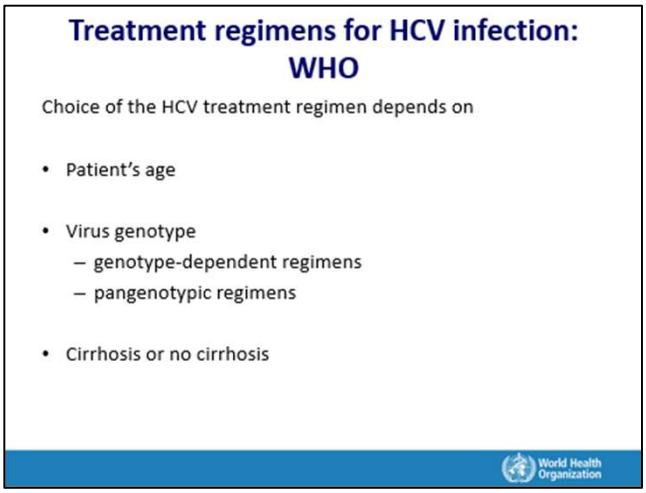
Each DAA medication attacks one of these targets; combination DAA tablets attack more than one target.

DAA medications are classified based on which mechanism they use against HCV.

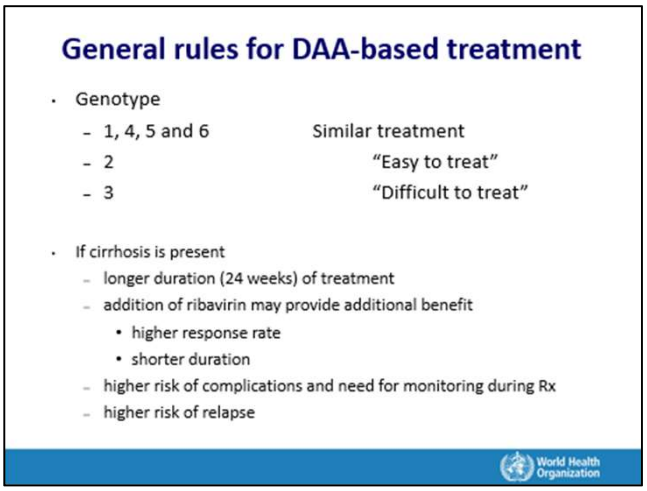
Recognizing the DAA medication classes becomes particularly important when re-treating a patient for HCV who has been previously treated with DAA-based therapy.



WHO recommends the use of the following DAAs for HCV treatment in different combinations.

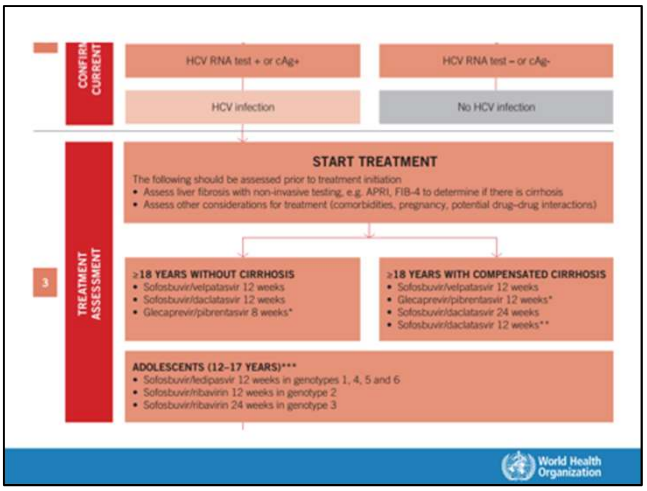


For every person who needs treatment for HCV infection, infection management will require information on age of the patient, genotype of the virus circulating in the host, and presence or absence of cirrhosis.

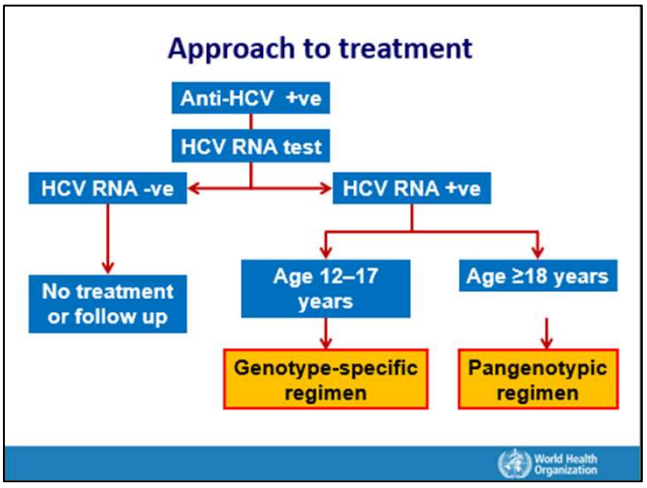


Earlier in the era of pegylated interferon, genotype 3 infection was considered difficult to treat. But in the present era of DAAs this is not true because DAAs are highly effective against genotype 3 as well.

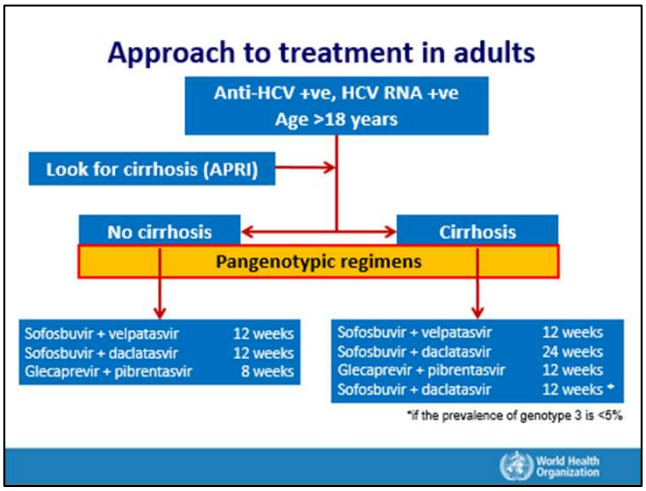
A HCV-infected person with cirrhosis needs a longer duration of treatment, may require ribavirin to either enhance the response or to reduce the duration of treatment, and will require lifelong monitoring for the complications of cirrhosis such as HCC after successful treatment.



We should divide treatment into 3 groups, those over 18 years with and without cirrhosis, and adolescents, i.e. those 12–17 years old. In the current guideline, treatment among the 3 groups is different.

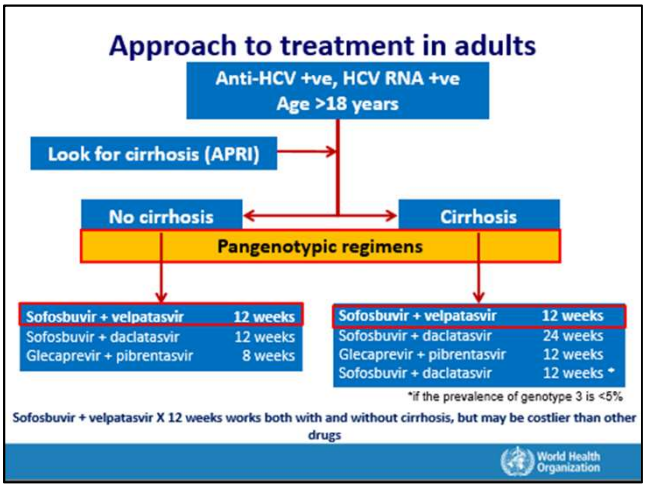


For patients who are HCV RNA positive, only genotypic-specific regimen is available for those aged 12–17 years, and pangenotypic regimen can be applicable for those over 18 years.

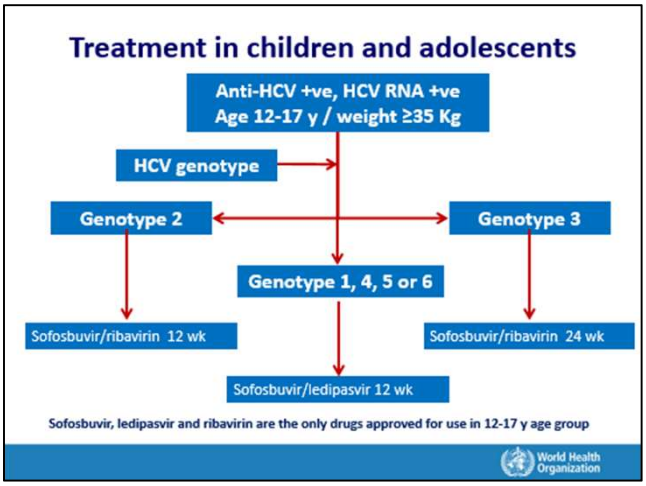


For a patient over 18 years, we should evaluate the patient for the status of cirrhosis.

Whether cirrhosis is present or absent, a pangenotypic regimen is applicable, however, the treatment duration is different in each group.



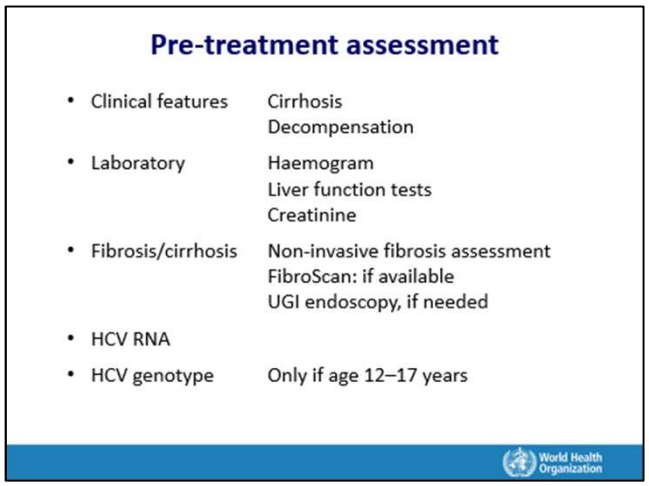
Sofosbuvir and velpatasvir for 12 weeks works both with and without cirrhosis, but may be costlier than the other drugs.



As we have discussed a while ago, only genotypic specific regimen is available for age 12-17 years.

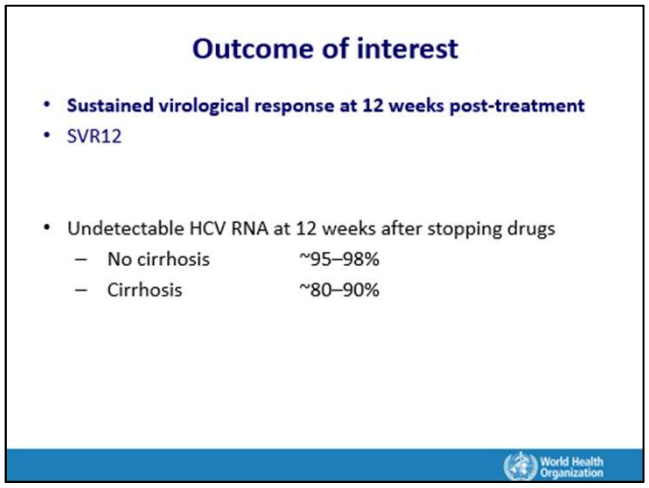
We should check HCV genotype and choose the regimen corresponding the genotype.

This is because Sofosbuvir, ledipasvir and ribavirin are the only drugs approved for use in 12-17 y age group.

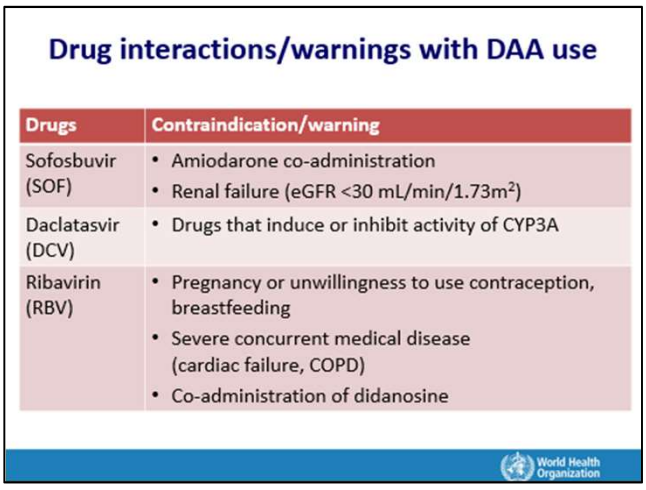


The evaluation of a patient, regardless of the pathogen (e.g. HCV in this case), includes two components: first, investigations to diagnose the condition, identify the pathogen and decide specific chemotherapeutic agents (e.g. Widal test and blood culture with antibacterial sensitivity in a patient with suspected enteric fever; HCV RNA and HCV genotype in an anti-HCV-positive person); second; the investigation to identify and assess adverse effects in the form of complications because of the identified pathogen (e.g. to evaluate every HIV-positive person for tuberculosis.

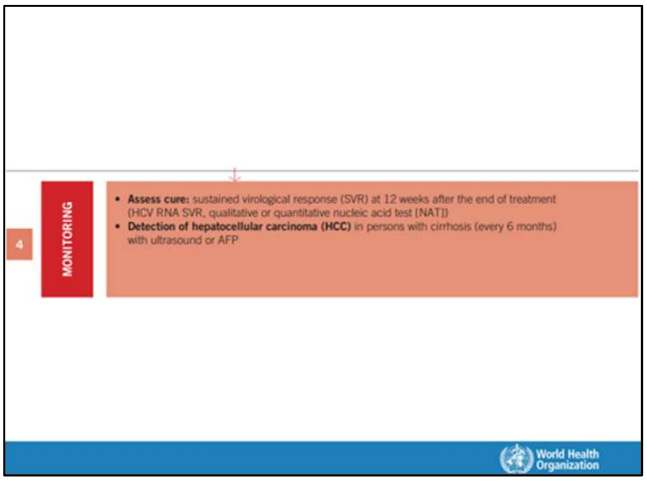
To assess the pathogen here, we need HCV RNA and HCV genotyping if the age is between 12 and 17 years; these tests should only be done if the administration of anti-HCV treatment is a possibility because these are very costly tests and may cost around US$ 1500 in a non-public-funded setting. Assessment for liver disease severity due to HCV is needed in every person regardless of treatment; these investigations include haemogram, LFT, ultrasound abdomen and endoscopic examination.



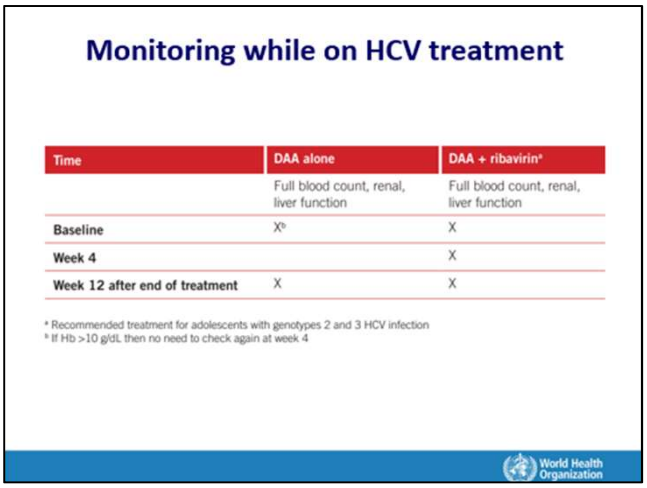
The success of DAA-based anti-HCV treatment is assessed by the sustained virological response rate after 12 weeks of stopping the treatment, which is also known as SVR12. SVR12 is achieved in 95–98% of people without cirrhosis but the rate is reduced to 80–90% in the presence of cirrhosis.



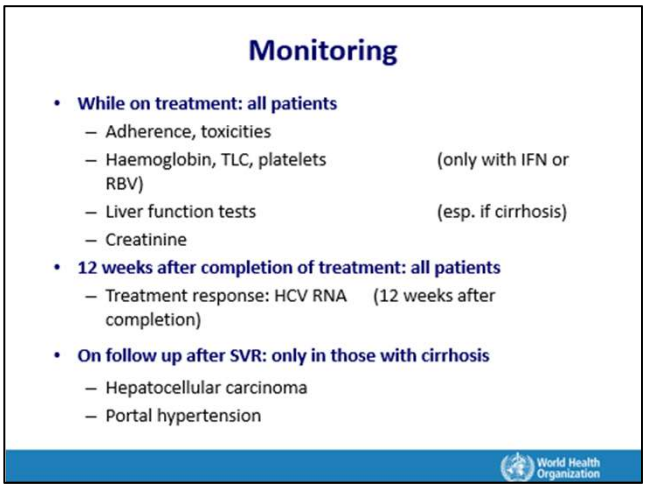
We should pay attention to drug interactions and warnings with DAA use. A few of the most important interactions are described here.



In the final phase, we should conduct monitoring. Assessing cure is necessary. We should make sure to confirm SVR 12. In addition, even though we can confirm SVR, detection of HCC is necessary in persons with cirrhosis. Therefore, we should conduct ultrasound or AFP in every 6 months.

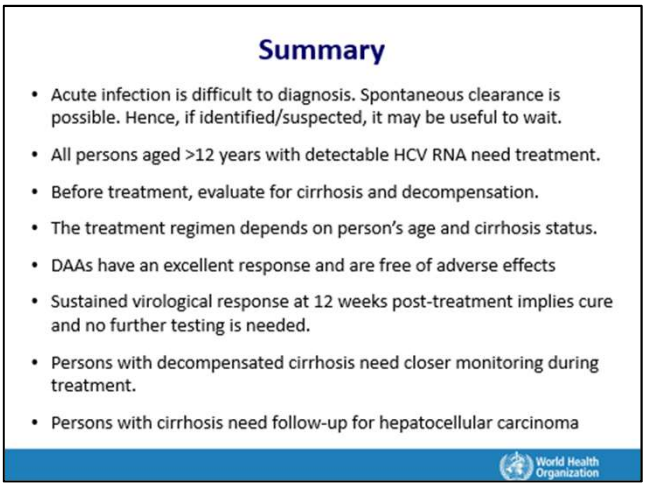


This slide shows how to monitor a person while on HCV treatment. We should monitor full blood count, renal and liver functions at baseline and week 12 after the end of treatment. In addition, these should be monitored at week 4, as well patients who take ribavirin or whose haemoglobin is under 10 g/dL.



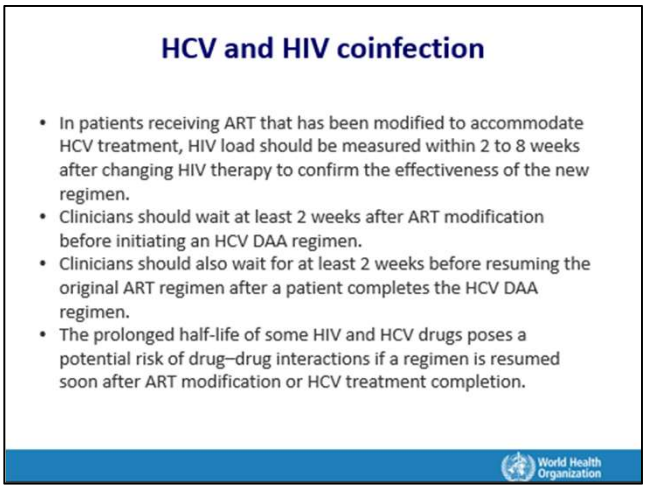
During treatment, every patient should be monitored for drug compliance, tolerance and toxicities, if any. After stopping treatment everyone will need an HCV RNA assay for SVR12. After achieving SVR12, non-cirrhotic patients need no further follow up but those with cirrhosis will need lifelong follow up for cirrhosis-related complications such as HCC, varices, hepatic encephalopathy, etc.

Module 15



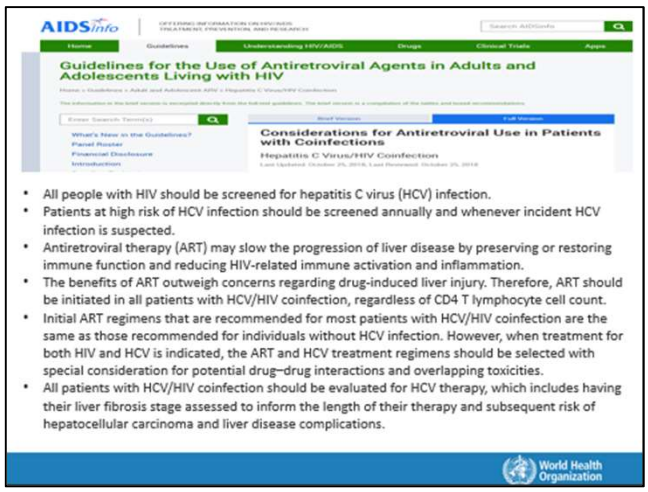
Acute infection with HCV is occasionally diagnosed and may clear spontaneously in a proportion of patients.

All those aged >12 years with active HCV infection should be treated according to the recommended treatment regimens. Currently available DAAs are highly effective and safe, and the majority of those treated will achieve SVR12. In the absence of cirrhosis, a person does not need any follow up after achieving SVR12.

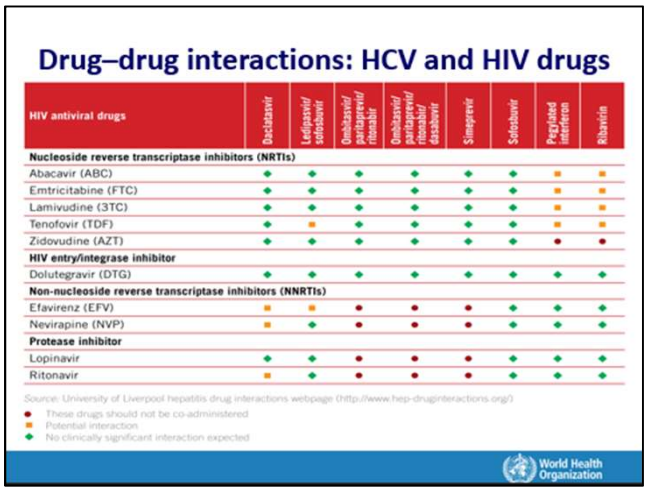


In the era of DAA use, HIV/HCV-coinfected people are not considered to be a "difficult-to-treat" group because in HCV/HIV-confected persons the treatment regimens, durations and the response (which is measured as SVR12) are similar to those with HCV monoinfection. In an HIV-coinfected person, drug-to-drug interactions between antiretroviral and anti-HCV drugs are very important and this may need some modification in treatment regimens.

A few important aspects should be kept in mind while dealing with an HCV/HIV-coinfected person. A few patients on antiretroviral drugs may need a change in ART regimen before starting anti-HCV drugs. In such patients, the efficacy of ART should be ensured before starting anti-HCV drugs; anti-HCV treatment should be started after at least 2 weeks of ART modification; ART should be reinstituted or modified to the pre-HCV treatment regimens after 2 weeks of stopping anti-HCV drugs.

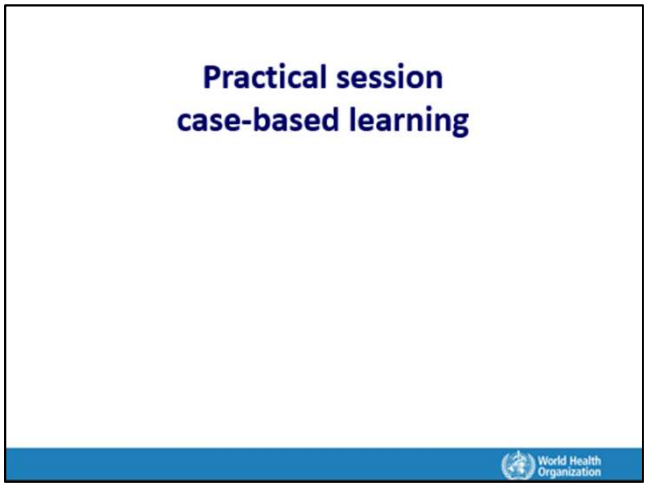


These are a few other important points that need mention in this presentation.

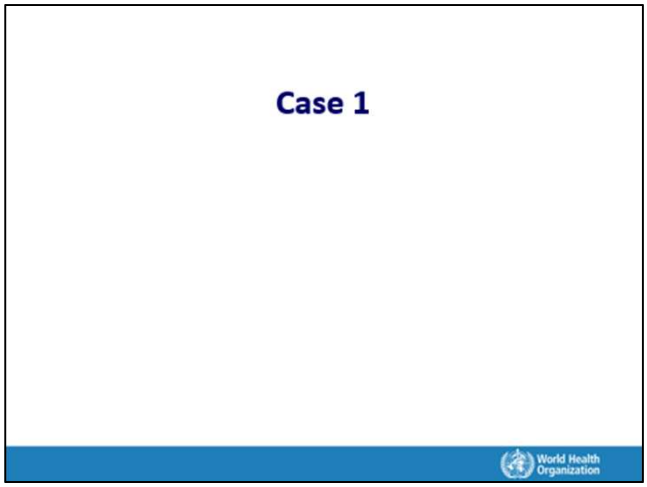


This slide shows the drug–drug interactions of HCV and HIV drugs.

The green marks mean that no clinically significant interaction is expected, therefore, we can prescribe safely.



Now we will do some practice sessions.



First case

Case 1

- A 52-year-old man presents with malaise
  - No previous illness
  - Examination: unremarkable
  - Investigations

ALT	**64 IU/L**	(normal <40)
AST	**88 IU/L**	(normal <40)
HBsAg	Negative	
Anti-HCV	**Positive**	

What further test would you order?

World Health Organization

A 52-year-old gentleman had a few nonspecific symptoms and was detected to be anti-HCV positive.

Case 1: laboratory test results

Investigations	Values
Haemoglobin (g/dL)	11.8
Platelets ($X10^9$/L)	98
Total bilirubin (mg/dL)	1.2
Albumin (g/dL)	3.4
AST (IU/L)	88 (normal <40)
Prothrombin time (INR)	1.6
HCV RNA quantitative (log_{10} IU/mL)	7.1
Ultrasound	Coarse echotexture of liver Portal vein diameter 14 mm Splenomegaly, no ascites

World Health Organization

His platelets were low, AST wa elevated and USG abdomen showed features of chronic liver disease or cirrhosis.

Case 1: management issues

- Is treatment recommended?
- What is the stage of liver disease?
  - cirrhosis versus no cirrhosis
  - compensated versus decompensated
- What regimen should one use?
- How would you monitor the patient during treatment?
- Does the patient require follow up after achieving SVR 12?

World Health Organization

These are the questions that we need to answer before starting treatment.

Case 1

Is treatment recommended?

HCV RNA is detectable. Hence, yes.

What is the stage of liver disease?

APRI = [88/40] x 100/98 = 2.2

APRI >2.0 → Liver cirrhosis (compensated)

Select the preferred recommended regimen

Sofosbuvir/daclatasvir for 24 weeks

Sofosbuvir/velpatasvir for 12 weeks

Glecaprevir/pibrentasvir for 12 weeks

How should the treatment be monitored?

For efficacy and decompensation

Follow up with screening for HCC: lifelong

World Health Organization

Case 2

World Health Organization

Case 2

- A 45-year-old woman
- Complaints: insomnia
  - No previous hospitalization
  - No alcohol, tobacco and substance use
  - Examination: unremarkable
  - Investigations

Hb	12.6 g/dL	
AST	34 IU/L	(normal <40 IU/L)
HBsAg	Negative	
Anti-HCV	**Positive**	

What tests would you order?

World Health Organization

Case 2: laboratory test results

Investigations	Values
Haemoglobin (g/dL)	9.8
Platelets (X10^9/L)	218
Total bilirubin (mg/dL)	0.8
Albumin (g/dL)	4.0
AST (IU/L)	34 (normal <40)
Prothrombin time (INR)	1.5
HCV RNA (log_{10} IU/mL)	6.4
Ultrasound	Liver normal size, echotexture Portal vein diameter 10 mm Spleen normal, no ascites

World Health Organization

Case 2

What is the stage of liver disease?

APRI = [34/40]x100/218 = 85/218 = 0.4
APRI <2.0 → No liver cirrhosis

Is treatment recommended?

HCV RNA is detectable.

Select the recommended preferred regimen

Sofosbuvir/daclatasvir for 12 weeks
Sofosbuvir/velpatasvir for 12 weeks
Glecaprevir/pibrentasvir for 8 weeks

What monitoring do you require?

Monitor during treatment. Ensure SVR 12.
No follow up is needed after SVR12 has been documented.

World Health Organization

Case 3

World Health Organization

Case 3

- 55-year-old woman
- Complaints: abdominal distension x 3 months
  - No previous hospitalization
  - No alcohol, tobacco and substance use
  - Examination: bilateral pedal oedema, splenomegaly, ascites
  - Investigations
    - Hb 10.6 g/dL
    - AST 76 IU/L (<40 IU/L)
    - HBsAg Negative
    - Anti-HCV **Positive**
- **What tests would you order?**

World Health Organization

Case 3: Laboratory test results

Investigations	Values
Hemoglobin (g/dL)	10.8
Platelets ($X10^9$/L)	75
Total bilirubin (mg/dL)	1.2
Albumin (g/dL)	2.8
AST (IU/L)	96 (normal <40)
Prothrombin time (INR)	1.9
HCV RNA (log_{10} IU/mL)	7.1
Ultrasound	Small, shrunken, nodular liver Portal vein diameter 14 mm Splenomegaly, moderate ascites

World Health Organization

Case 3

What is the stage of liver disease?

APRI = [96/40] x 100/75 = 3.2

APRI >2.0 → Liver cirrhosis

Compensated or decompensated cirrhosis?

Ascites present >> decompensated cirrhosis

Is treatment recommended?

HCV RNA is detectable. Hence, yes.

Select recommended preferred regimen

Refer to a higher centre.

World Health Organization

Case 3

What is the stage of liver disease?

APRI = [96/40] x 100/75 = 3.2
APRI >2.0 → Liver cirrhosis
Ascites present >> **decompensated cirrhosis**

Is treatment recommended?

HCV RNA is detectable. Hence, yes.

Select the recommended preferred regimen

Refer to a higher centre.

What monitoring does she require?

Monitor **for decompensation** and efficacy (SVR 12).
Follow up with screening for **HCC – lifelong.**

World Health Organization

Treatment: patient with advanced liver disease

- Longer treatment duration
- Need for ribavirin
- Need for supportive treatment (for ascites, varices, etc.)
- Poor drug tolerance, especially ribavirin
- Worsening of liver disease
- Poorer response Lower SVR 12
  Higher risk of relapse
- Need follow up for complications of cirrhosis, even after SVR

World Health Organization

Case 4

- 15-year-old girl
- Incidentally detected HCV positive
  - No previous hospitalization
  - Examination: nno abnormality detected
  - Investigations
    - Hb 12.6 g/dL
    - AST **76 IU/L** (<40 IU/L)
    - HBsAg Negative
    - Anti-HCV **Positive**

- **What tests would you order?**

World Health Organization

Case 4: laboratory test results

Investigations	Values
Haemoglobin (g/dL)	12.6
Platelets ($X10^9$/L)	245
Total bilirubin (mg/dL)	0.8
Albumin (g/dL)	4.0
AST (IU/L)	76 (normal <40)
Prothrombin time (INR)	1.0
HCV RNA (log_{10} IU/mL)	6.4
Ultrasound	Liver normal size, echotexture Portal vein diameter 10 mm Spleen normal, no ascites

World Health Organization

Case 4

What is the stage of liver disease?

APRI = [76/40] x 100/245 = 0.80

APRI <2.0 → No liver cirrhosis

Is treatment recommended?

HCV RNA is detectable.

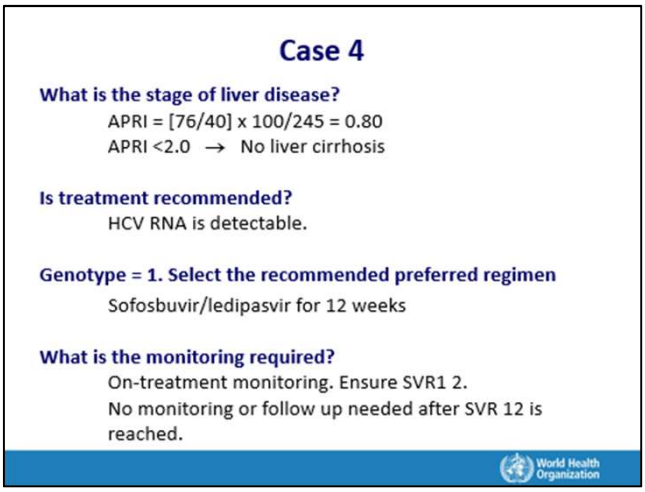
Select the recommended preferred regimen

World Health Organization

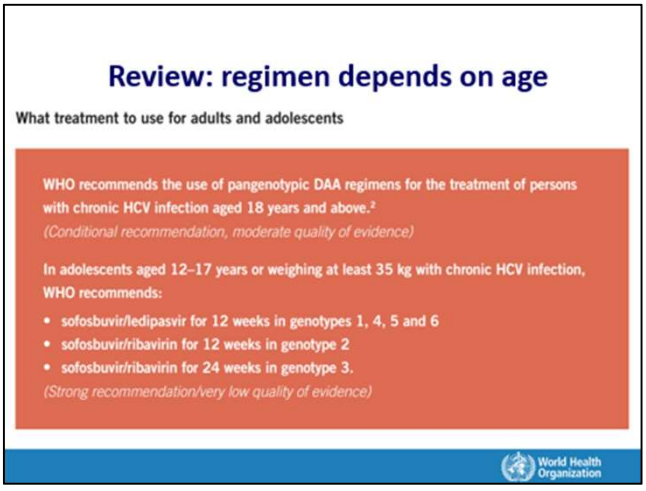
Case 4

- For age 12–17 years, only sofosbuvir, ledipasvir and ribavirin are approved.
- Ledipasvir is a genotype-specific drug.
- Hence, genotype testing is needed.

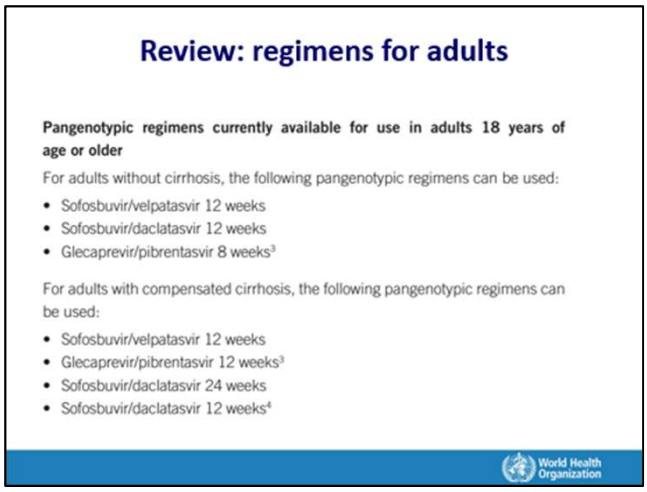
World Health Organization



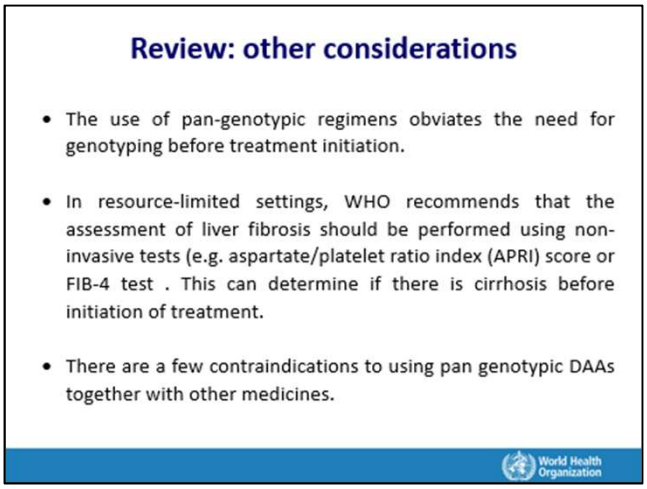
All those with active HCV infection and who are at least 12 years of age should be considered for treatment.



For adults, pangenotypic regimens are to be used while for children between 12 and 17 years, a genotype-specific regimen has to be used.



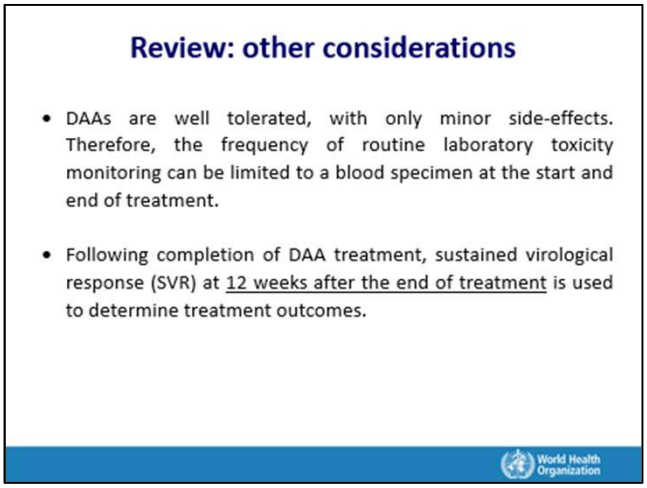
These are the pangenotypic regimens recommended for adults with or without cirrhosis.



Before starting treatment, liver fibrosis should be assessed with simple tests such as APRI or FIB-4. Pangenotypic regimens are preferred.

The DAAs have very few side-effects and need very limited monitoring while on treatment.

Treatment response should be ascertained with SVR12.



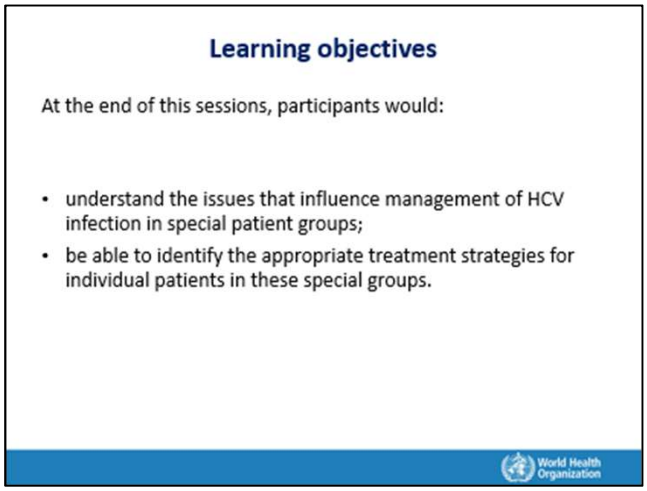
Before starting treatment, liver fibrosis should be assessed with simple tests such as APRI or FIB-4. Pangenotypic regimens are preferred.

The DAAs have very few side-effects and need very limited monitoring while on treatment.
Treatment response should be ascertained with SVR12.

Module 16

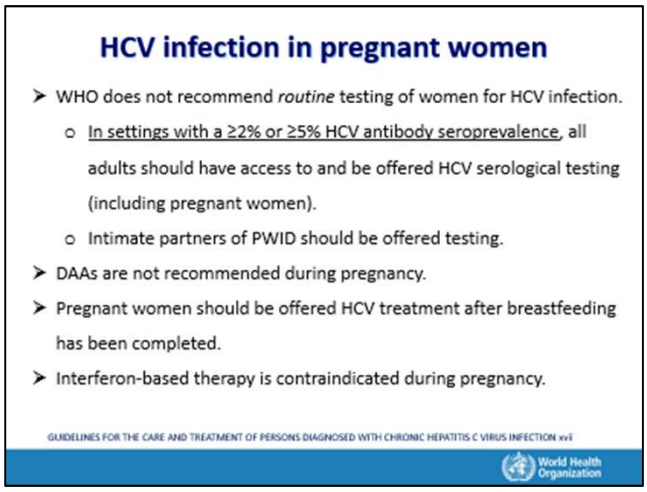
Treatment of HCV infection in special situations

Module 16



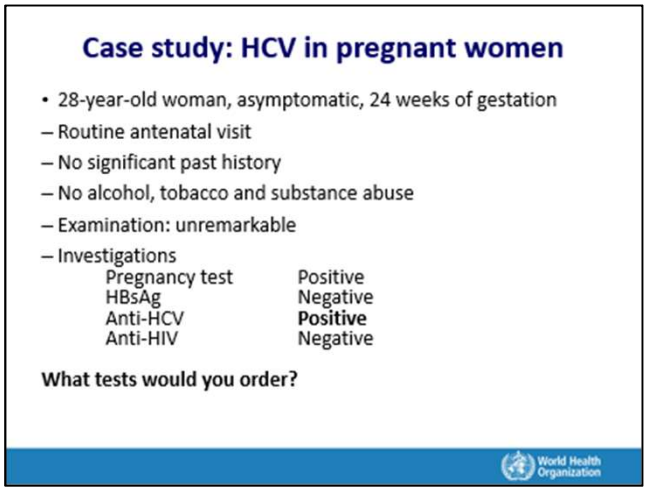
After this session, we would be able to identify the issues in the management of special populations, evaluate them, choose the appropriate treatment regimen and follow them.

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



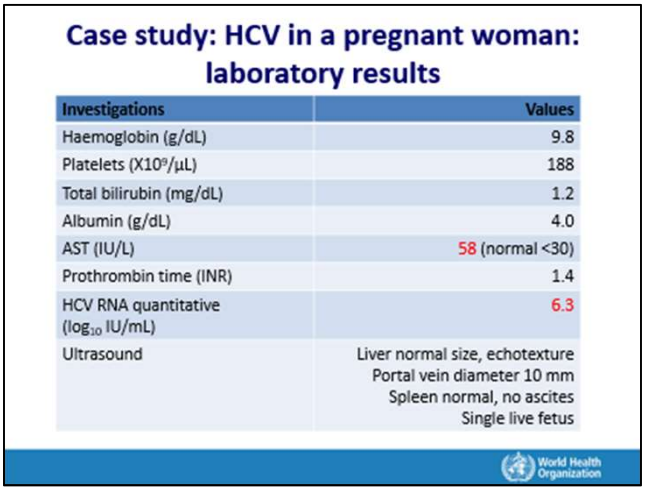
Routine screening of pregnant women for anti-HCV is not recommended. One of the major reasons for this is that direct acting antiviral (DAA) drugs are not approved for use in pregnancy. A pregnant woman, if found to be HCV viraemic infected (confirmed HCV infected), should continue her pregnancy. Breast feeding is recommended as part of infant feeding choices. There is no evidence of HCV mother-to-child transmission from breastfeeding. Caesearan 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.



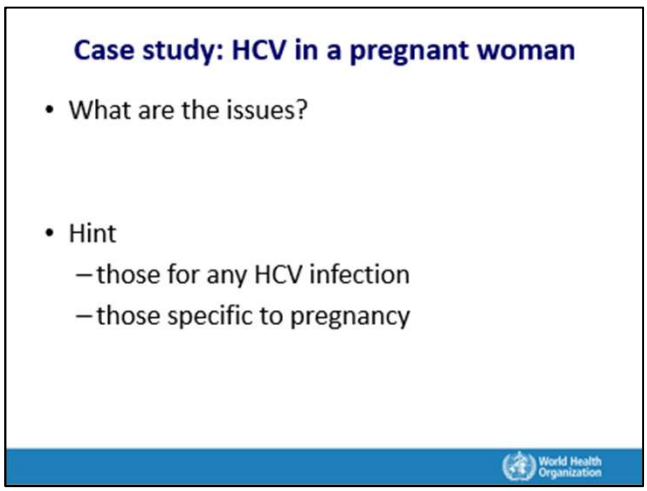
A 28 years old pregnant women was found to be anti-HCV positive in her third trimester.

How to approach this lady?

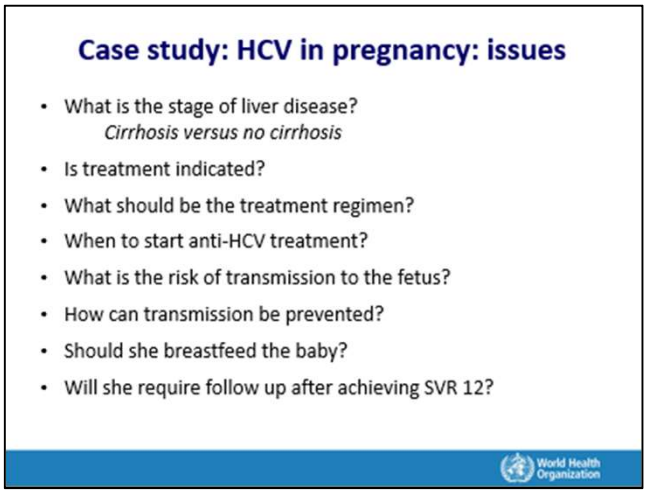


Laboratory evaluation revealed elevated ALT HCV RNA. USG abdomen showed no evidence of cirrhosis.

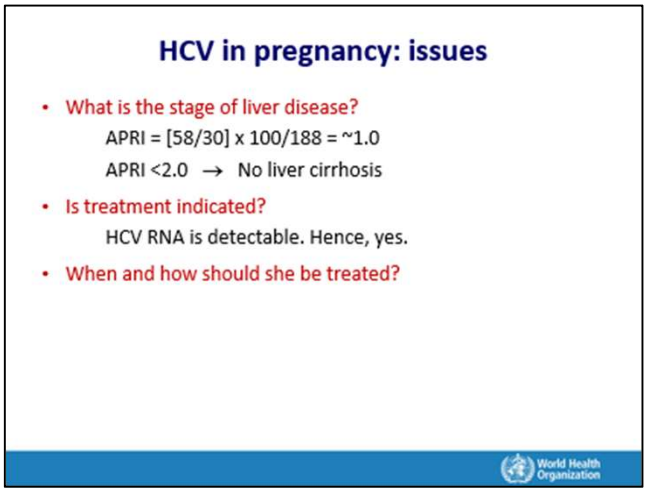
What next?



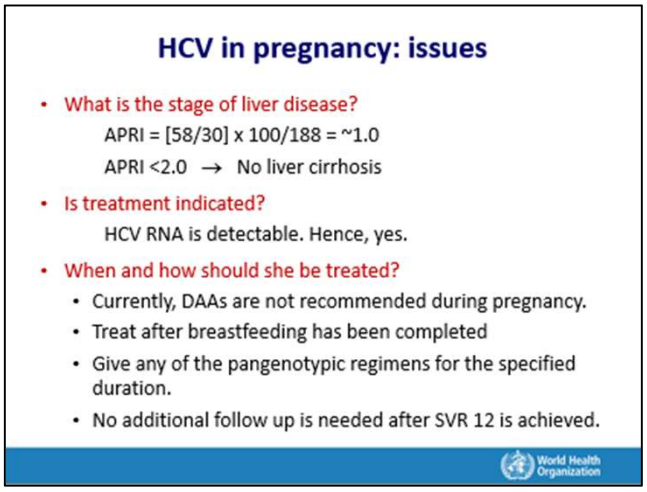
We need to identify the issues that are related HCV infection in a background of pregnancy.



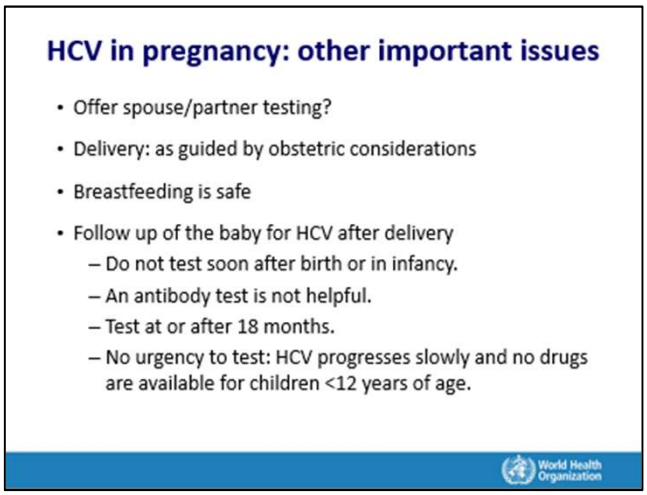
These are the issues in an anti-HCV-positive pregnant woman.



She does not have cirrhosis.
RNA is detectable hence anti-HCV treatment will be needed.
When could we start anti-HCV treatment?



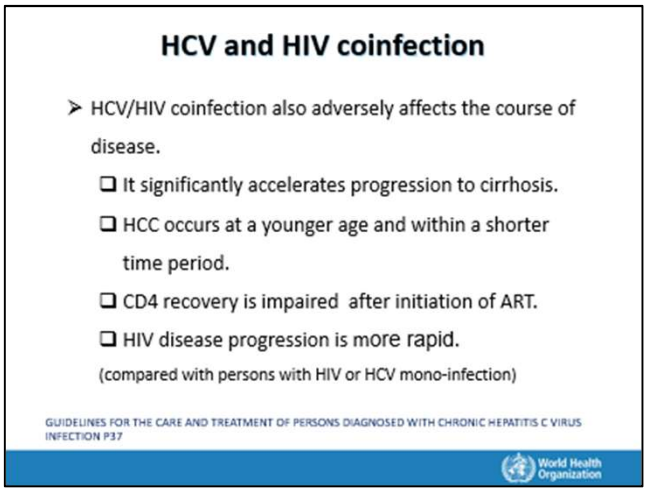
Because DAAs are not approved for use in pregnant women and lactating mothers, she can be treated with a pangenotypic regimen after breastfeeding is completed. In the absence of cirrhosis, she will not need any follow up after achieving SVR 12.



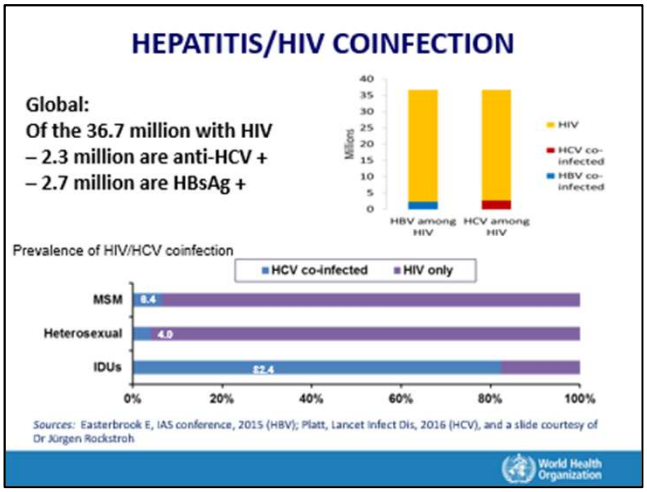
There are a few additional issues that must be communicated.
First, spouse testing should be considered. Spouse testing is considered because of the ease and benefit of treatment. The risk of HCV transmission between spouses is very low. Hence, if treatment is not a possibility, spouse screening should 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-enteral 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.

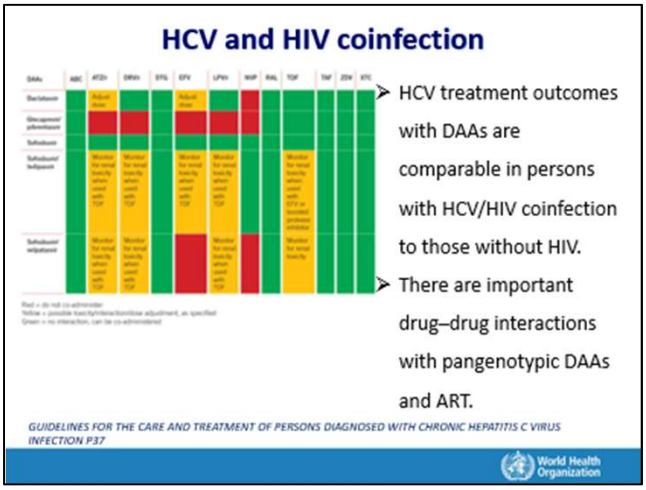


HCV and HIV adversely affect the natural history of each other. In the presence of HIV infection, the rate of progression to cirrhosis and risk of HCC are increased, though the response to anti-HCV DAAs is not affected. Similarly, in the presence of HCV infection, the rate of HIV progression is increased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



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.

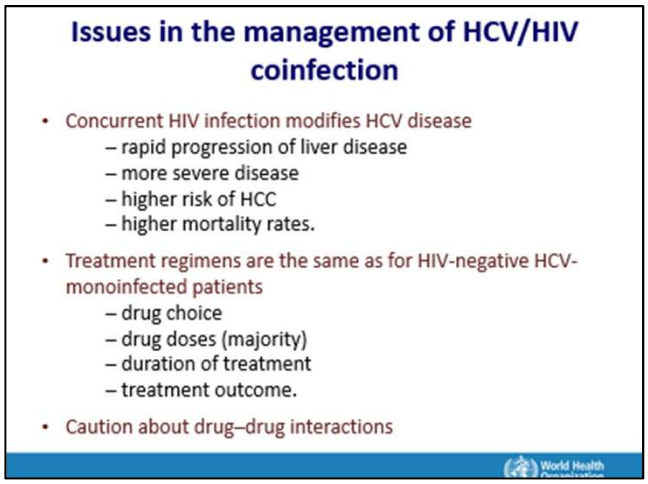
Module 16



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.

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.



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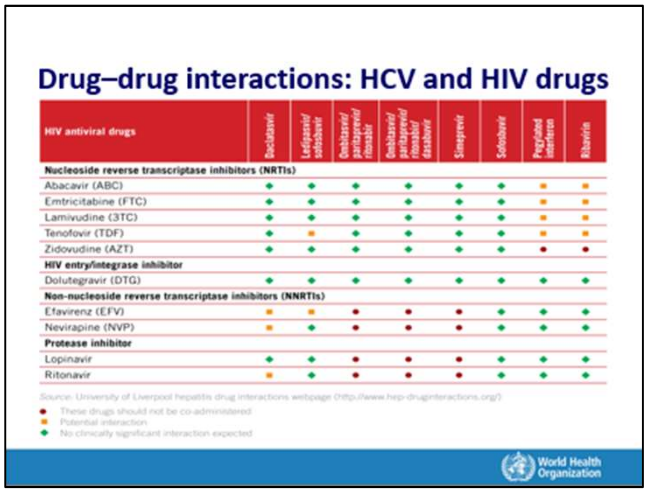
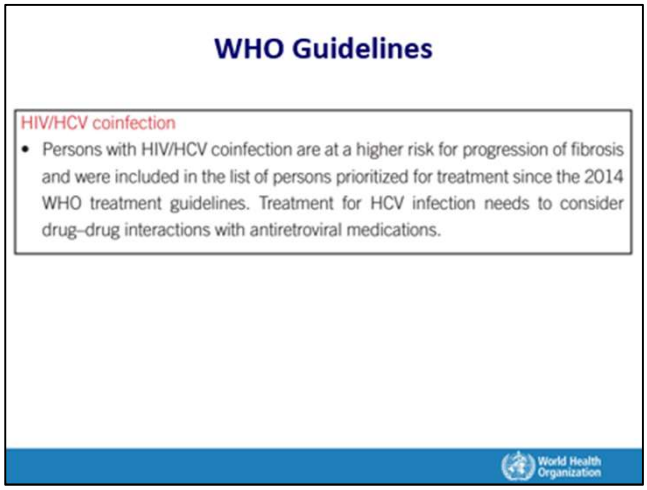
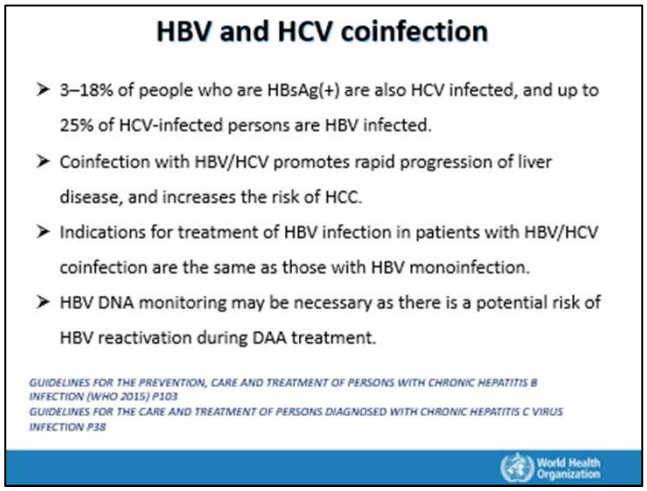


These are a few of the most commonly encountered drug-to-drug interactions between ART and HCV drugs.

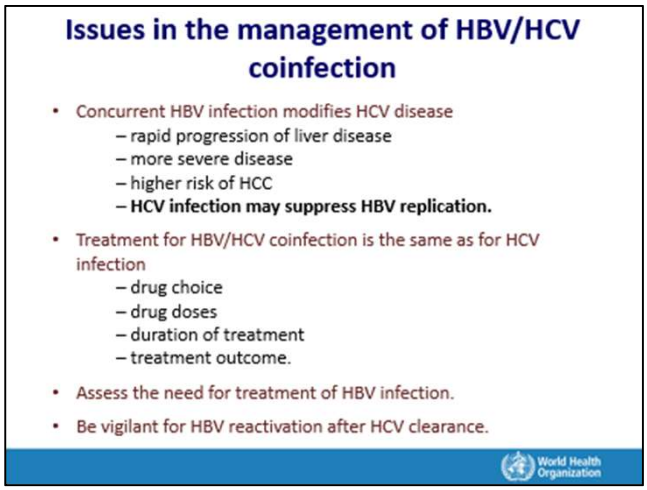


Because of rapid progression of liver fibrosis in HIV/HCV-coinfected persons, their treatment should be prioritized in resource-constrained settings.

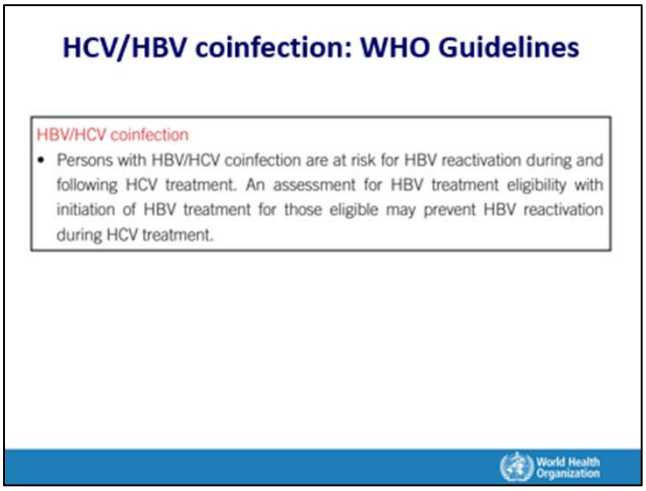


It is not uncommon to see HBV and HCV coinfection. This situation is more common among certain high-risk groups such as those with HIV, those who inject drugs, or those on maintenance haemodialysis.

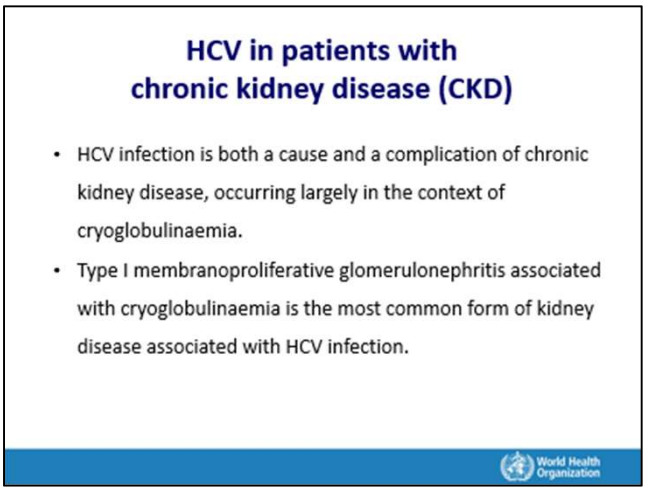
Both HBV and HCV are hepatotropic viruses and cause liver injury. Hence, their coinfection results in relatively rapid progression of liver disease and adverse outcomes.



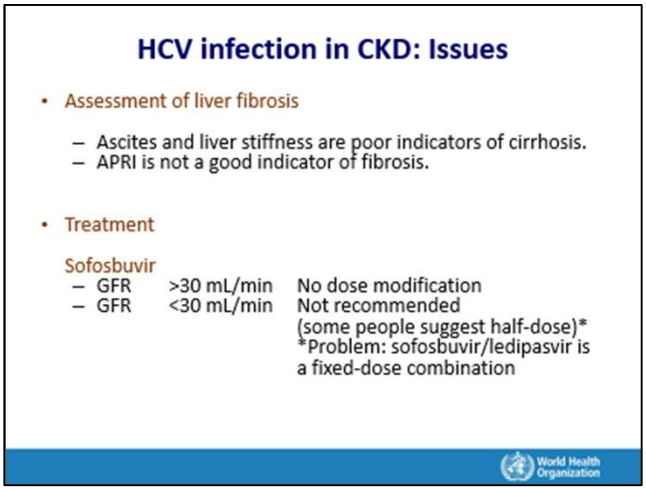
HBV or HCV treatment indications, drugs of choice, duration, etc. are similar to those in monoinfected persons. In most coinfected people, HCV is actively replicating while HBV remains dormant. Successful HCV treatment may lead to reactivation of HBV, which can be detected with careful monitoring.



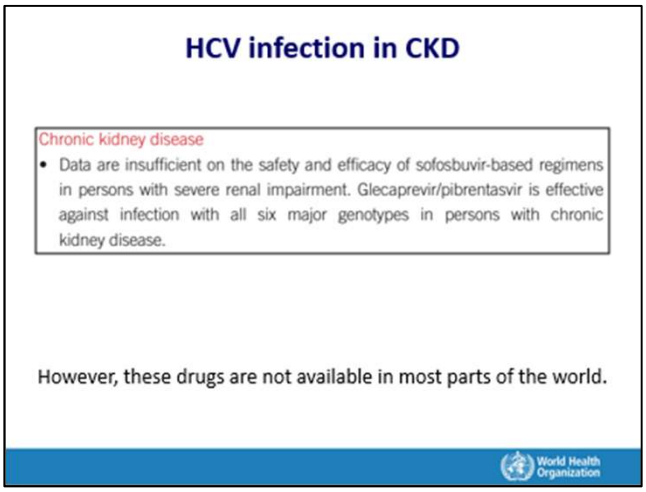
The risk of HBV reactivation after HCV treatment is recognized by WHO as well, and we need to actively look for it during follow up after HCV treatment.



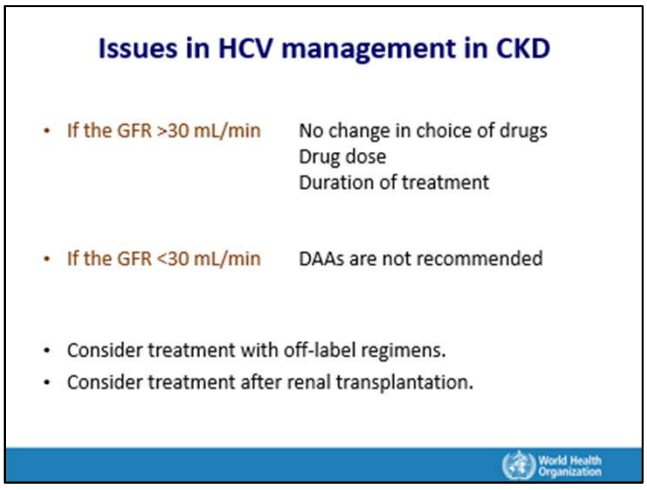
HCV infection and chronic kidney disease (CKD) have a mutual interaction with each other. HCV infection increases the risk of CKD. HCV-related CKD may or may not be secondary to cryglobulinaemia. Similarly, the risk of HCV infection is increased in the presence of CKD. This risk is much more in those 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 toimpaired dialysis hygiene.



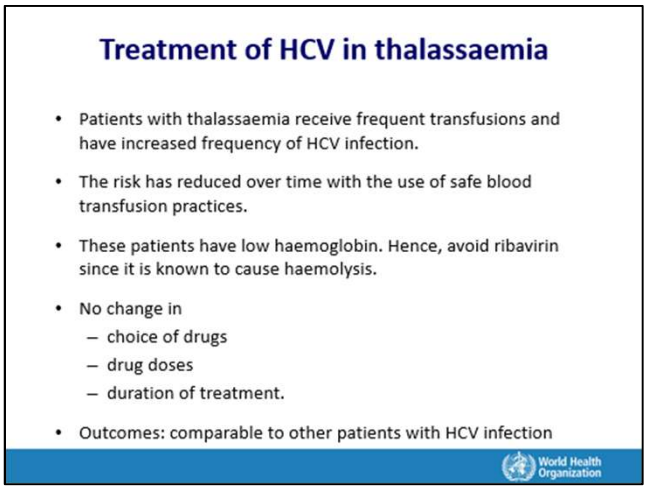
We will understand the important issues in the assessment and management of HCV in a patient with CKD, in particular, those with a glomerular filtration rate (GFR) below 30 mL/min. Till now, we have learnt that APRI is the most common measure for assessing liver fibrosis but this index does not work 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.



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.

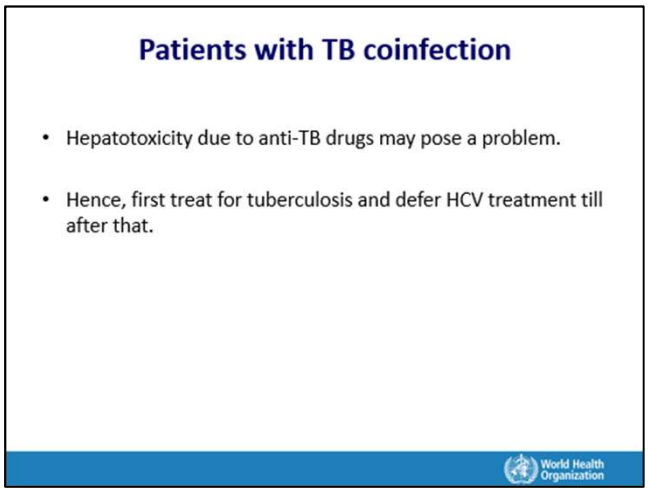


For those with a GFR below 30 mL/min, we need either off-label use of sofosbuvir or plan HCV treatment after renal transplantation.



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.

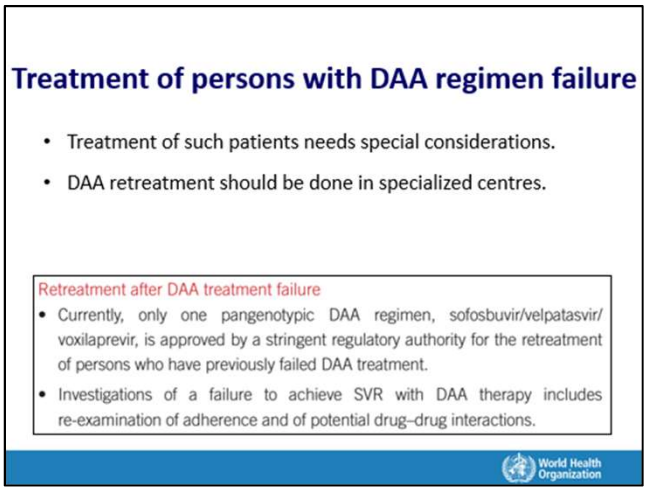
We have keep this in mind while treating HCV infection in such patients. These patients have a low level of haemoglobin. Hence, ribavirin should never be used in such patients because ribavirin causes haemolysis, which could be life-threatening for such patients.



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.



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.

World Health Organization

Module 17

WHO Monitoring and Evaluation Framework for Viral Hepatitis

Learning objectives

At the end of this session, learners would understand:

- the public health response to viral hepatitis
- the Global Health Sector Strategy on Viral Hepatitis and its service and impact targets for the year 2030
- various aspects of WHO's Monitoring and Evaluation Framework for Viral Hepatitis, and reporting towards the WHO Global Reporting System for Hepatitis (GRSH)

World Health Organization

THE GLOBAL HEALTH SECTOR STRATEGY ON VIRAL HEPATITIS

5 STRATEGIC DIRECTIONS

1. **Information for focused action**
2. Interventions for impact
3. Delivering for equity
4. Financing for sustainability
5. Innovation for acceleration

7th
leading cause of death globally (2013)

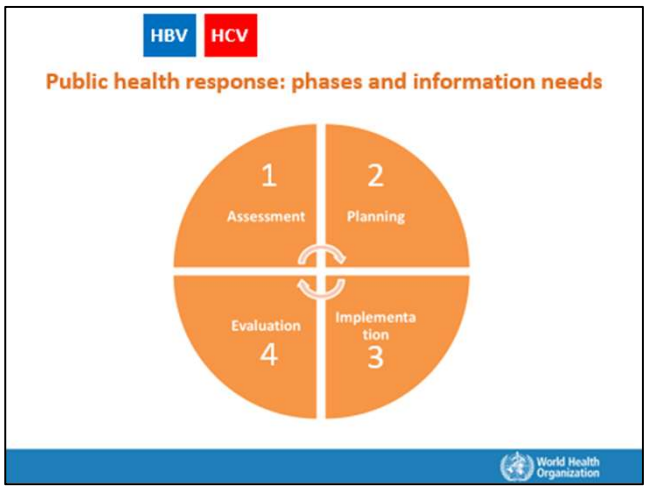
World Health Organization

Four main hepatitis viruses

A	E	B	C
Faecal–oral route		Exposure to blood/body fluids	
Acute hepatitis			
		Chronic infections	
		Sequelae	

95% of burden

World Health Organization



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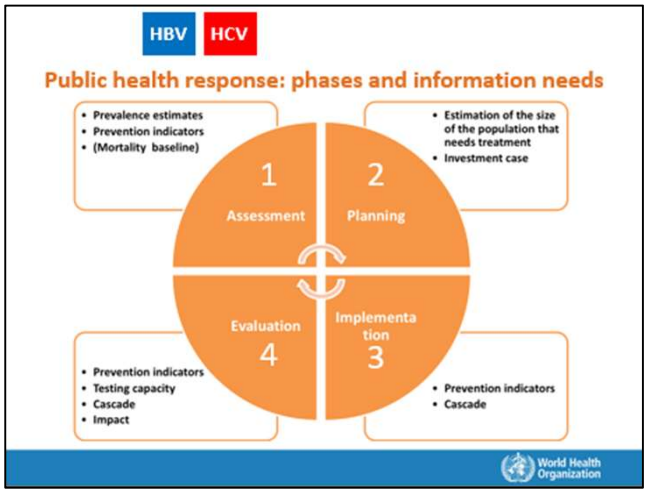

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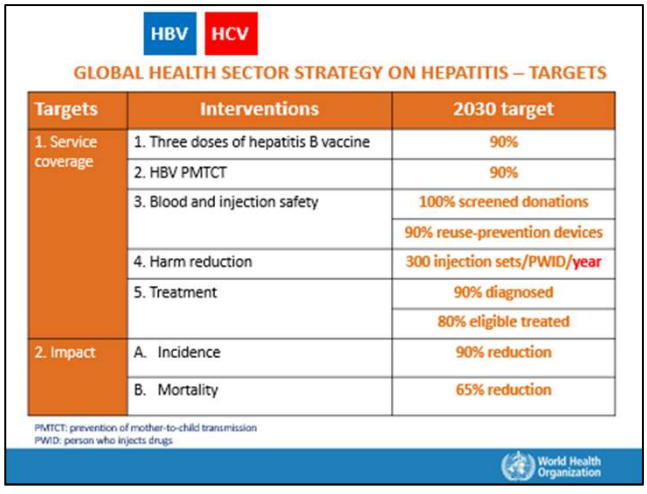
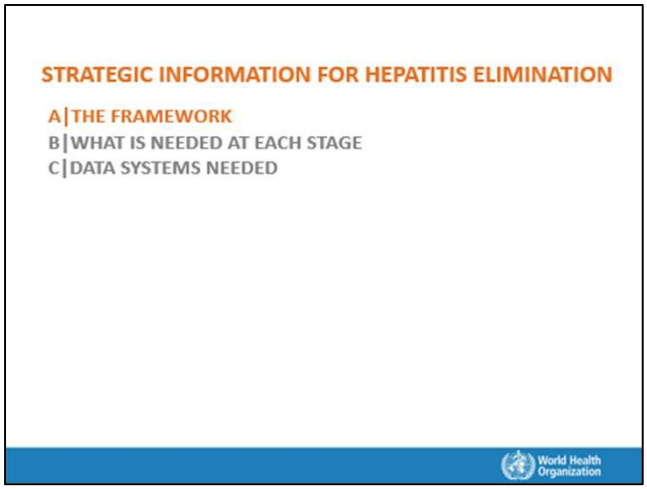


One of the reasons we do viral hepatitis surveillance is to evaluate programmes. Each of the three domains of viral hepatitis surveillance will help us evaluate different types of programmes.

First, information from surveillance for acute hepatitis can be used to evaluate programmes to prevent new infections, which includes vaccination, food and water safety, blood safety, condom distribution, harm reduction and infection control.

Second, information from surveillance for chronic hepatitis can be used to evaluate programmes for testing and treatment.

Third, information from surveillance of sequelae can be used to evaluate the ultimate impact a programme on mortality.



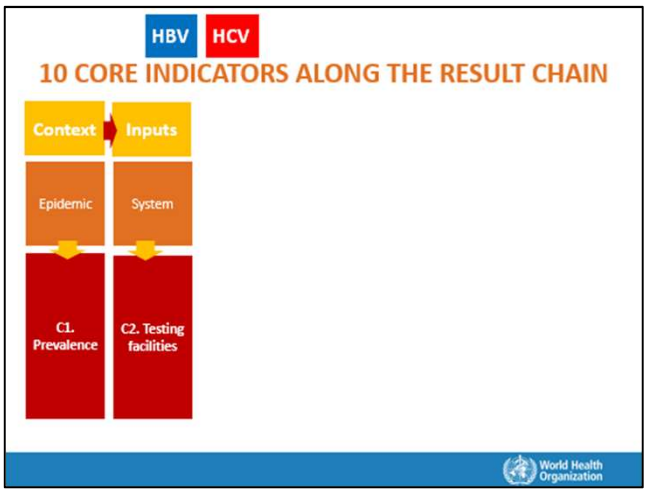
In a given country, there will usually be an existing system for viral hepatitis surveillance. For this reason, WHO suggests to improve the existing system rather than creating a new system. The steps to improve the system are the following:

First, make an inventory of what is already there. This may include some form of acute hepatitis surveillance or ad hoc surveys that estimated the prevalence of HBV or HCV infection.

Second, obtain some estimates of HBV and HCV prevalence. One needs to identify opportunities to coordinate surveys, for example with HIV or DHS surveys.

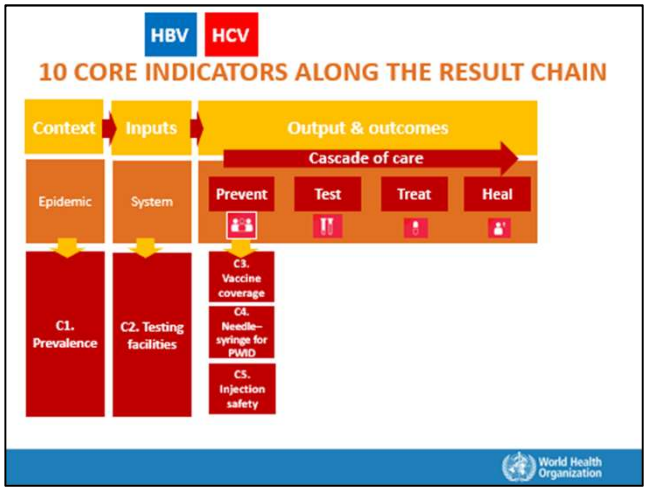
Third, optimize surveillance for acute hepatitis, which may include syndromic surveillance for acute hepatitis to detect outbreaks or sentinel surveillance for type-specific viral hepatitis.

When these three points are reasonably covered, it make sense to examine options to obtain data on sequelae.



This slides shows the 10 core indicators for viral hepatitis along the **result chain.** At the top of the slide, in light orange, you can see the **progression from context, to input, to output and outcome, and finally impact.** The **context and needs** will inform about epidemic patterns, stigma and population in need. The key indicators (C1) are the prevalence of HBV and HCV infection.

The **input** will inform about policy, laws, health systems, input and financing. The key indicator (c2) is about the infrastructure for testing. Then, we enter the **cascade of prevention and care**, including prevention, testing, care and treatment and cure / viral suppression. Prevention indicators measure vaccination (C3), needle and syringe distribution (C4) and injection safety (C5). Then, the cascade of testing, care and treatment is reflected by C6 (proportion of persons diagnosed), C7 (initiation [HCV] or coverage [HBV] of treatment) and C8 (cure [HCV] or viral suppression [HBV]). **The result based framework finishes with impact indicators**, including (a) incidence of HBV and HCV infection (C9) and (b) mortality (C10).



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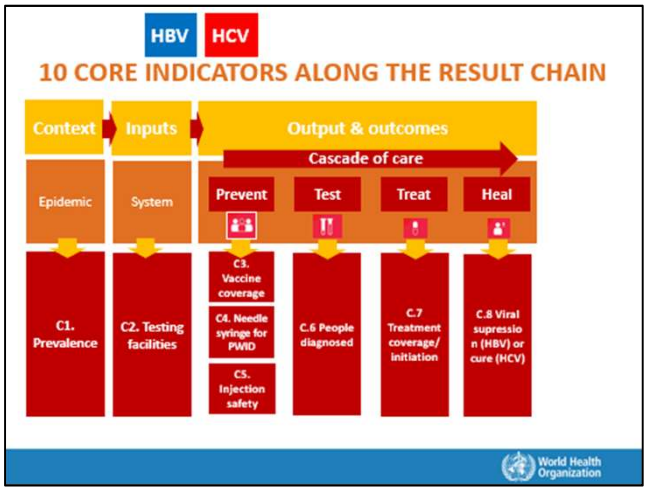
Module 17



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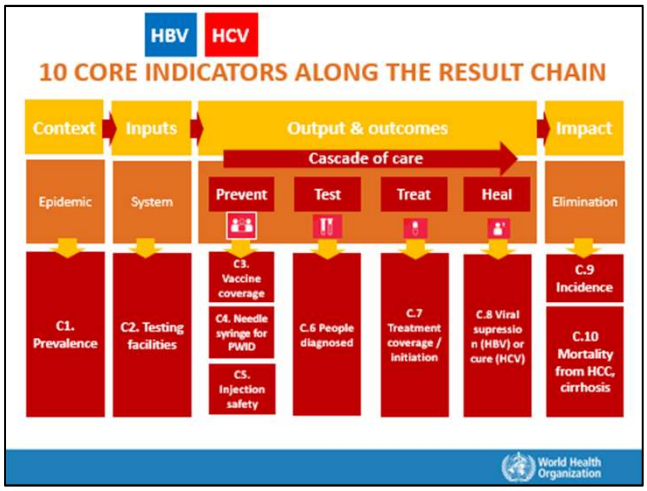

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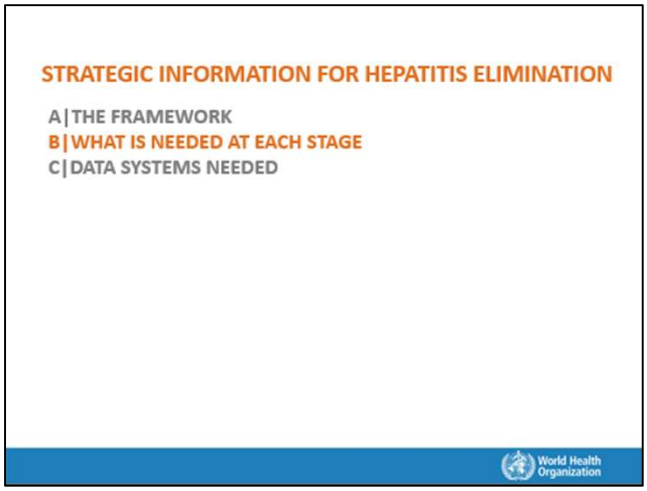

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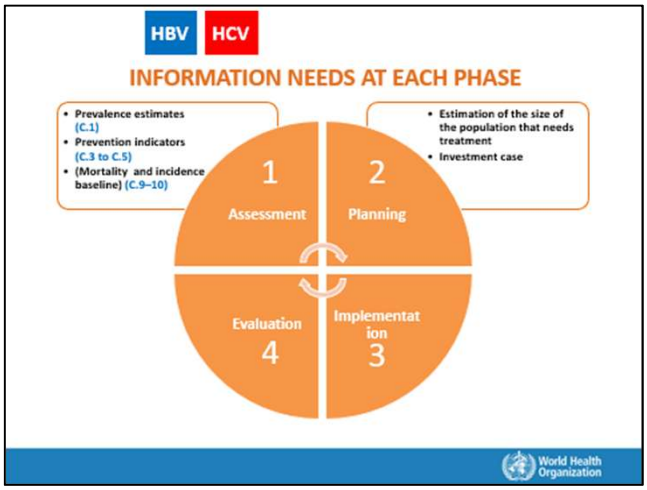

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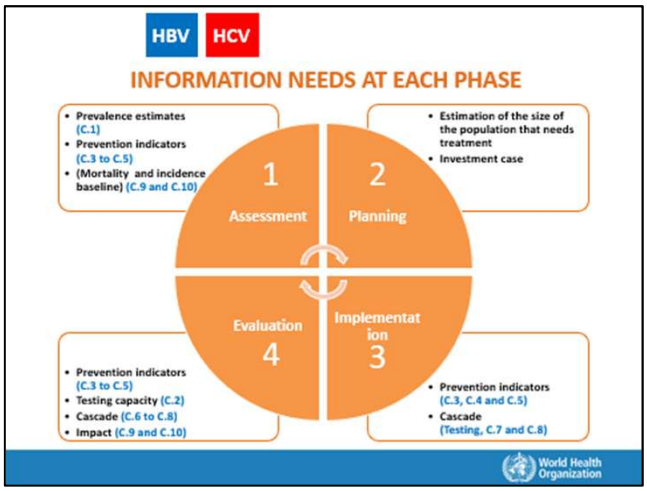

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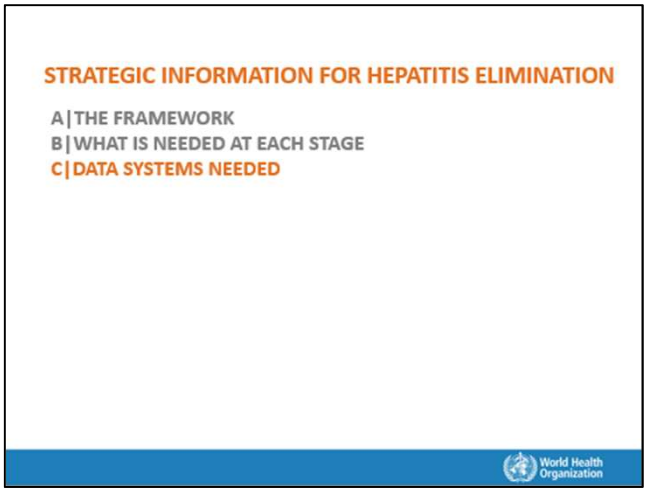

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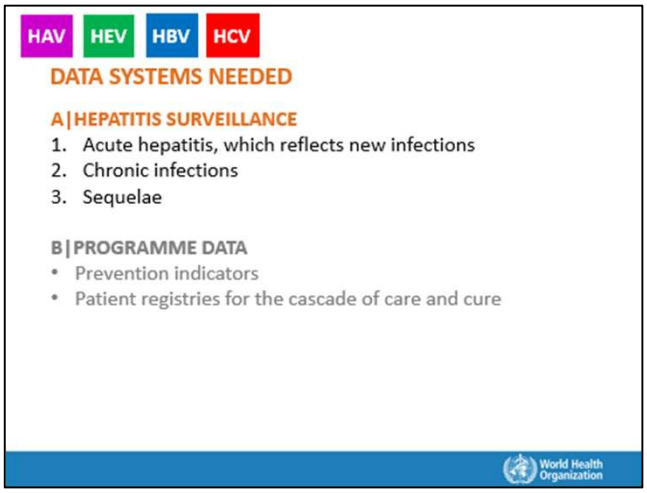

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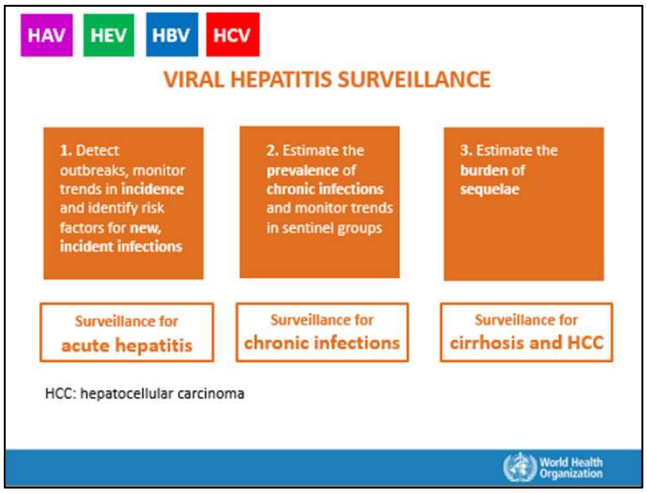
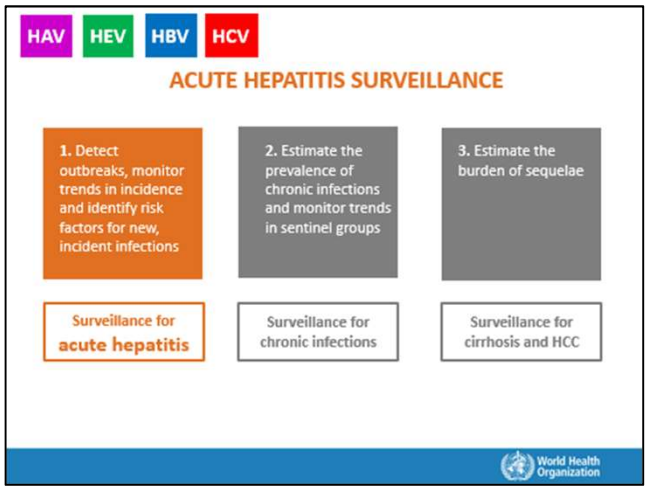
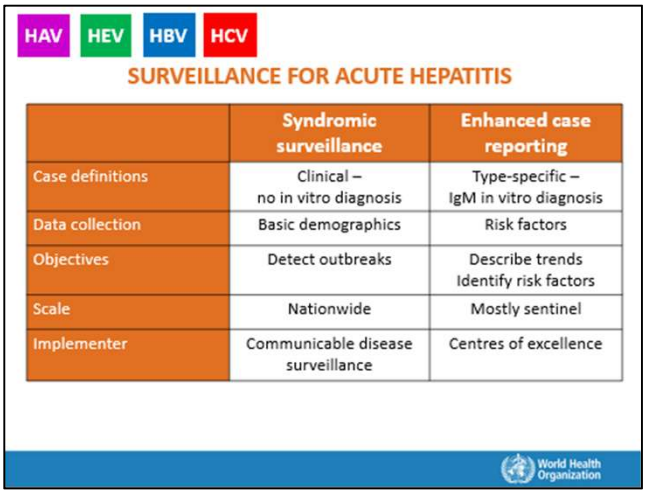


We tried to prepare this new document in a way that would help understanding why we do surveillance. In fact, viral hepatitis surveillance has three purposes.



The first purpose is to detect out outbreaks, monitor trends in in incidence and identify risk factors for new, incident infections. **This will be done with surveillance for acute hepatitis.**

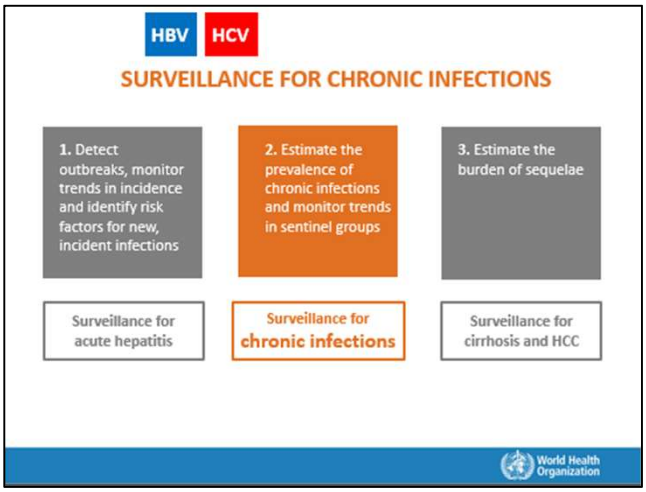


One of the reasons we do viral hepatitis surveillance is to evaluate programmes. Each of the three domains of viral hepatitis surveillance will help us evaluate different types of programmes.

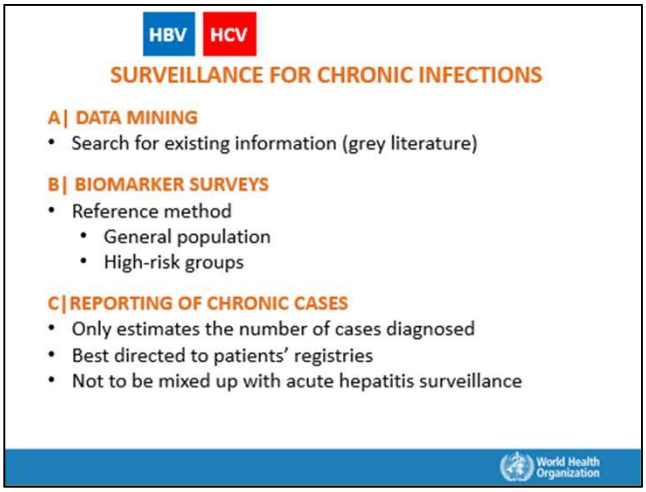
First, information from surveillance for acute hepatitis can be used to evaluate programmes to prevent new infections, which includes vaccination, food and water safety, blood safety, condom distribution, harm reduction and infection control.

Second, information from surveillance for chronic hepatitis can be used to evaluate programmes for testing and treatment.

Third, information from surveillance of sequelae can be used to evaluate the ultimate impact a programme on mortality.



The second purpose is to estimate the prevalence of chronic infections and monitor trends in sentinel groups. **This will be done with surveillance of chronic infections .**



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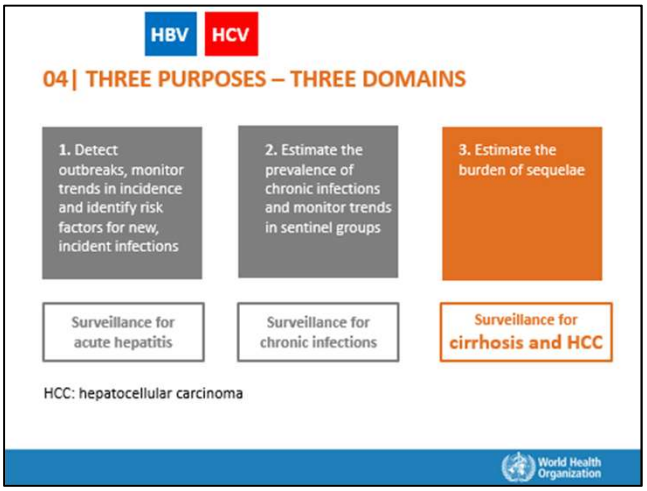

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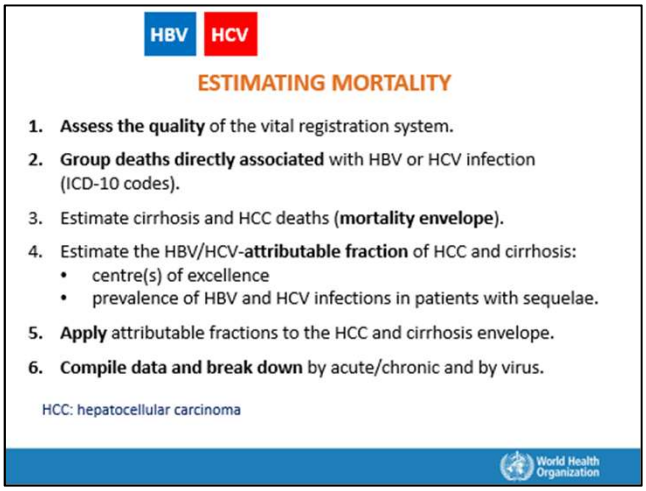

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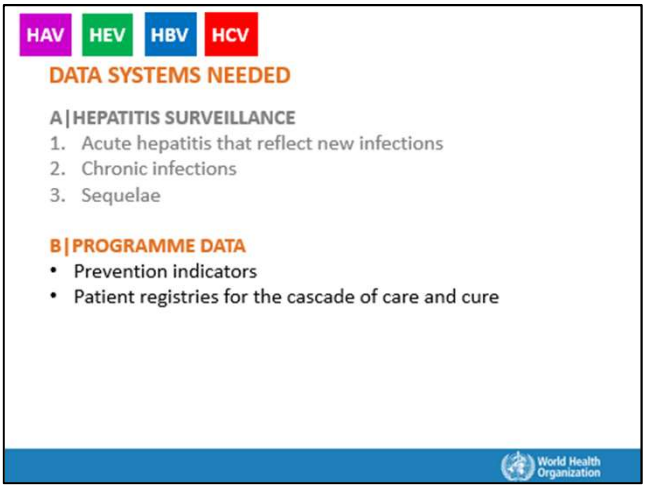

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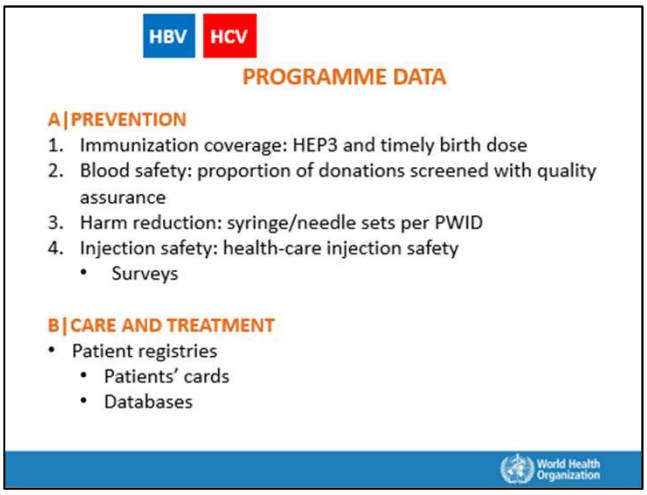

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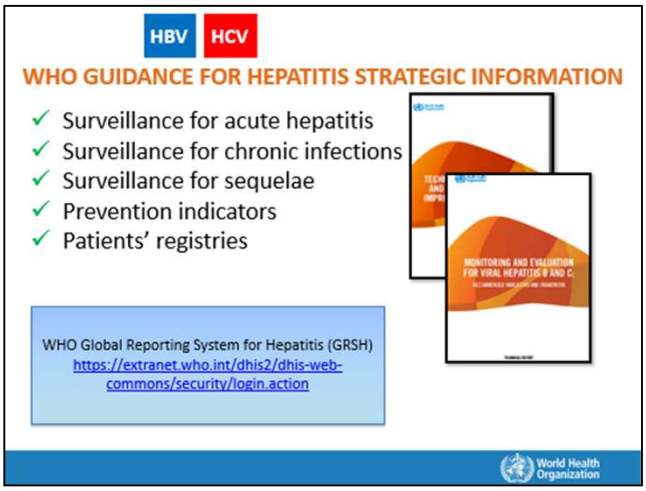

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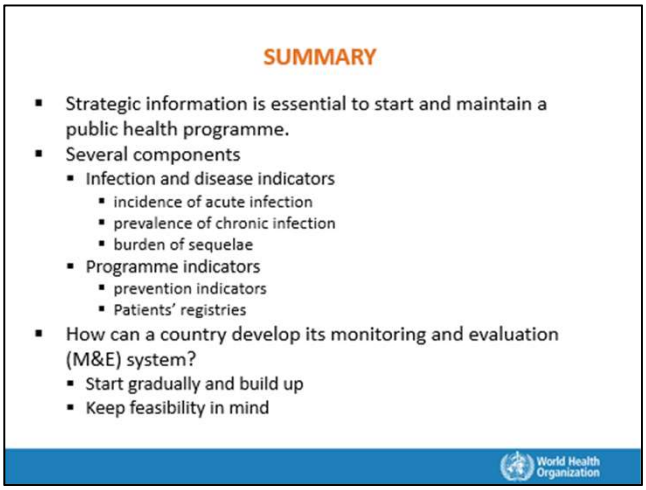
When these three points are reasonably covered, it make sense to examine options to obtain data on sequelae. WHO launched the Global Reporting System for Hepatitis (GRSH) for national reporting which supports reporting back towards SDGs on hepatitis elimination.



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Thank you

World Health Organization

HBV HCV

TYPE OF INDICATORS

10 CORE indicators C.1–C.10

27 ADDITIONAL indicators A.1–A.27

10 ADDITIONAL indicators for hepatitis (A.1–A.10)

17 ADDITIONAL indicators from other programmes (A.11–A.27)

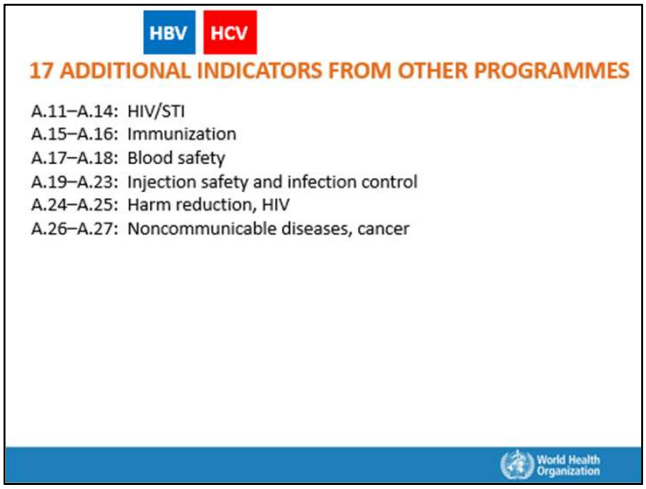
World Health Organization

HBV HCV

10 ADDITIONAL INDICATORS FOR HEPATITIS (A.1–A.10)

1. Hepatitis D coinfection among people living with HBV infection
2. Experience with discrimination
3. Availability of essential medicines and commodities
4. National system for viral hepatitis surveillance
5. Hepatitis B testing
6. Hepatitis C testing
7. HCV genotyping
8. Viral hepatitis B and C care coverage
9. Equitable access to hepatitis treatment
10. Documentation of treatment effectiveness

World Health Organization


HBV
HCV
17 ADDITIONAL INDICATORS FROM OTHER PROGRAMMES
A.11–A.14: HIV/STI
A.15–A.16: Immunization
A.17–A.18: Blood safety
A.19–A.23: Injection safety and infection control
A.24–A.25: Harm reduction, HIV
A.26–A.27: Noncommunicable diseases, cancer
World Health Organization