Antiviral therapy for Chronic hepatitis B

Hepatitis B Free

March 2024

Hepatitis B Free

Learning objectives

- Understand the antiviral therapies available
- Who to treat
- How to treat
- How to monitor
- Understand how tenofovir works, dosing and adjustments in renal impairment

Contents

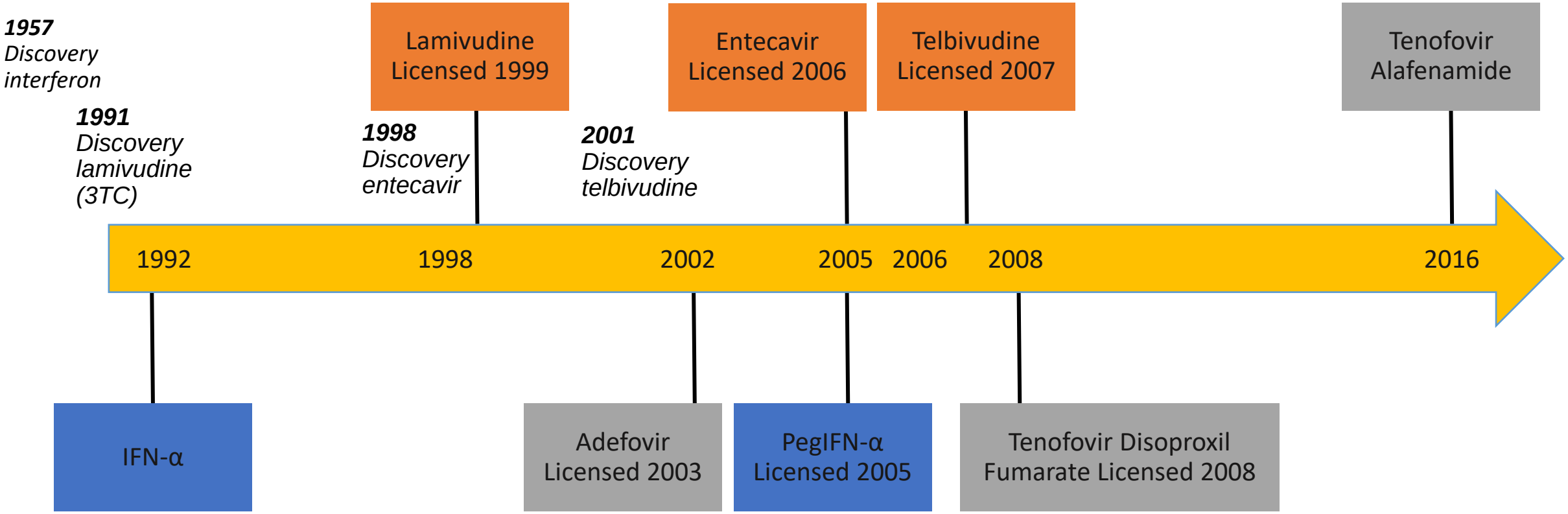
- Treatment of CHB
- Tenofovir
- History of antiviral therapy
- Mechanisms of action of antiviral therapy
- Management in patients with renal impairment

HOPE Kiribati

- Update

- What have we achieved to date..

The Evolution of HBV Therapy



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Treatment of CHB

Antiviral treatment

- Drugs with high potency, low barrier to resistance
- Easily tolerated
- Cheap
- Safe in cirrhosis
- Nucleos(t)ide analogue (NA):
  - Tenofovir disoproxil fumarate
  - Tenofovir alafenamide
  - Entecavir

Pegylated (PEG) –IFN

WHO recommended first line HBV Rx: Essential medicines list

Tenofovir Disoproxil Fumarate (TDF)	Tablet: 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)	- Listed in the adult WHO EML for hepatitis B: standard dose. - NOT listed in the WHO EML for hepatitis B for children and adolescent. - Approved by US FDA in 2012: 300 mg once daily oral for ≥12 years of age (≥35kg) with hepatitis B
Entecavir	Oral liquid: 0.05 mg/ mL Tablet: 0.5 mg or 1 mg	- Oral liquid for children (weight-based dose) up to 30 kg. Entecavir approved for children age ≥2 years. - Usual dose (adults): 0.5 mg/d oral for compensated liver disease. 1 mg/d for decompensated liver disease (0.5 mg x 2 pills daily)

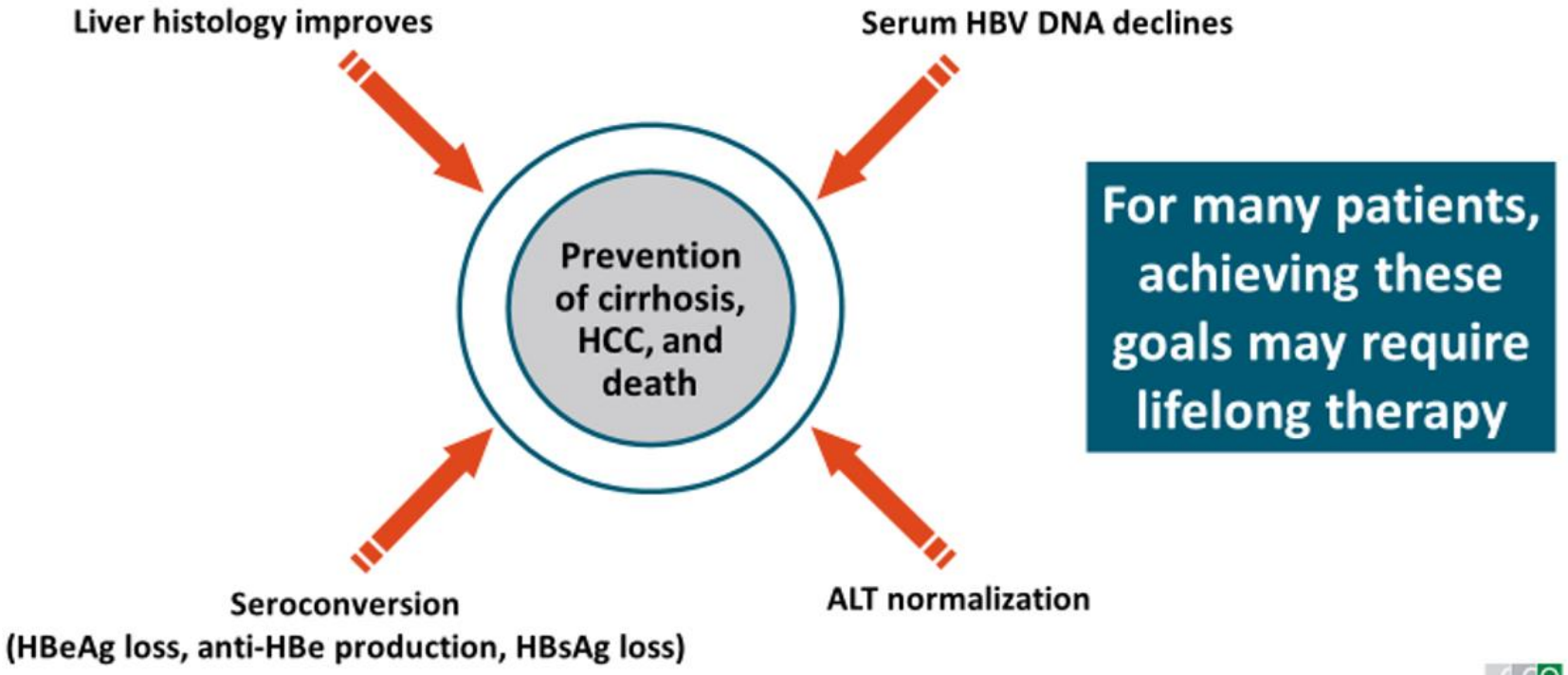
EML: essential medicines list

WHO Model List of Essential Medicines 20th List (March 2017) (Amended August 2017): adults, children

Antiviral therapy (TDF/ETV)

- Safe, well tolerated with minimal side effects
- Easy to take (one tablet per day in those with normal renal function)
- Reduces immune mediated inflammation and fibrosis (ALT decline)
- Achieves sustained viral suppression (HBV DNA), but does not offer cure and hence require long term (in some cases life long) treatment
- Leads to reversal of cirrhosis
- Reduces risk of liver cancer, progression to cirrhosis and improves survival
- Licensed generics available at <USD$4 per month

Goals of therapy



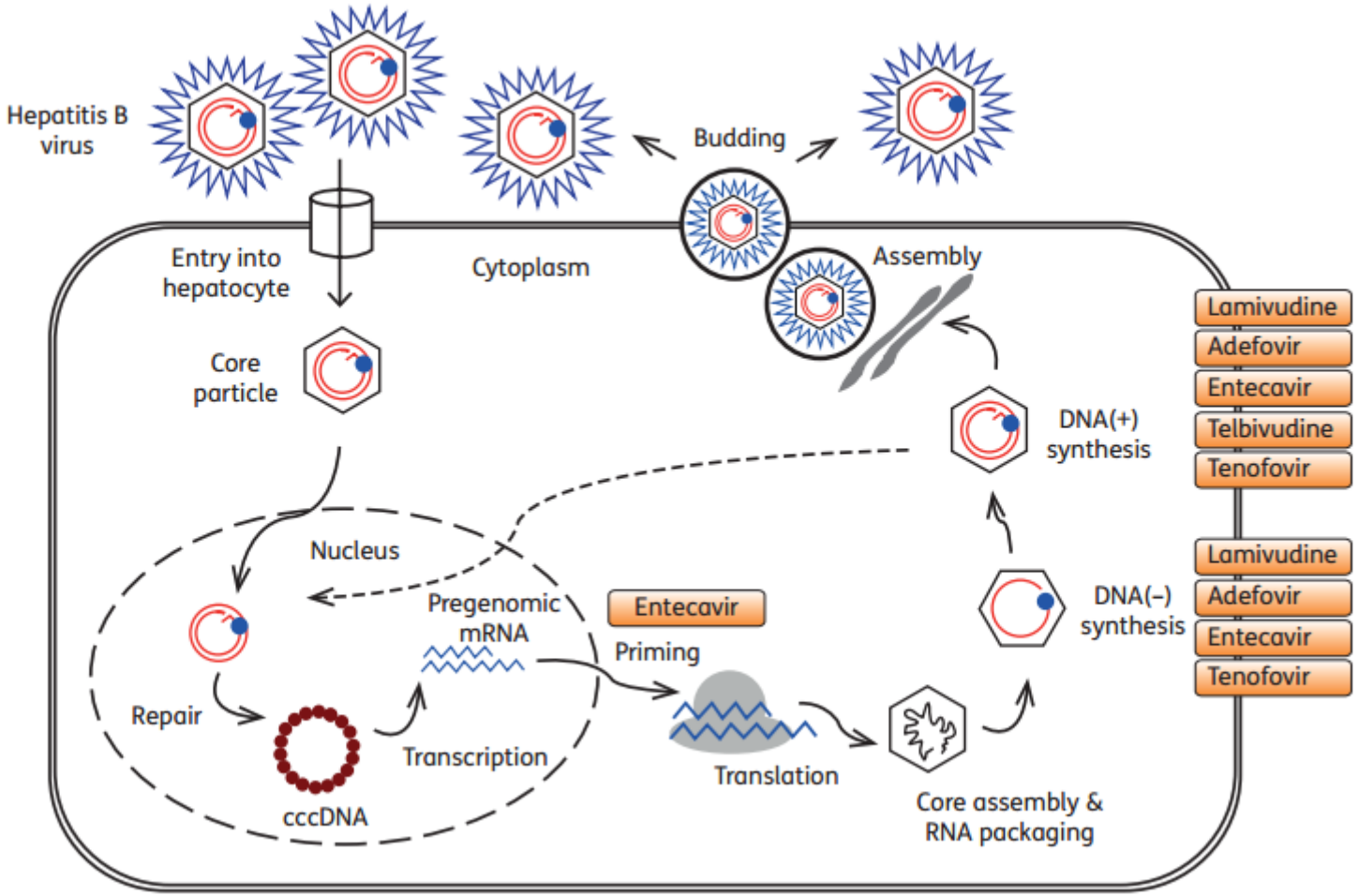
For many patients, achieving these goals may require lifelong therapy

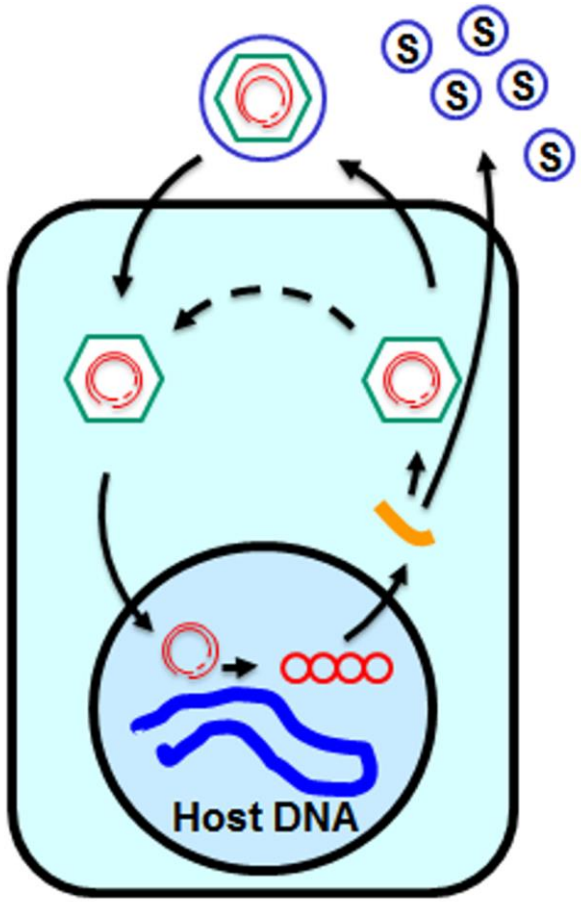
Slide credit: clinicaloptions.com

Reduce transmission: vertical transmission

Prevent reactivation

The replication cycle of HBV and sites of action of NAs





Who to treat

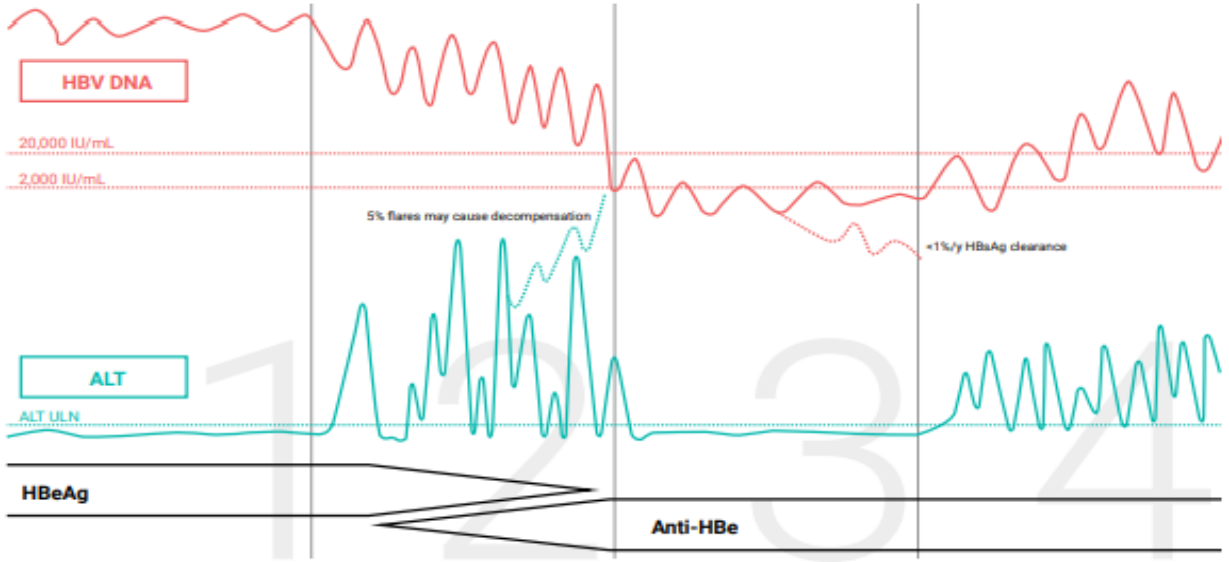
- All cirrhotic patients
- Cirrhosis based on:
  - Decompensation
  - APRI
  - FIB 4 score
  - Fibroscan
  - Ultrasound
- ss
- Those at risk of disease progression: age, sex, family history, ALT, coinfection, comorbidites
- Prevention of mother to child transmission
- Health care workers

DECISION MAKING IN HEPATITIS B

HBV

5 Assess phase of infection

Patients with CHB must be **regularly re-evaluated** to determine which phase they are in and managed accordingly.



HBeAg-positive chronic infection (Immune tolerance)	HBeAg-positive chronic hepatitis (Immune clearance)	HBeAg-negative chronic infection (Immune control)	HBeAg-negative chronic hepatitis (Immune escape)
• **HBV DNA: high†** >10^7 IU/mL • **ALT: normal** • **HBeAg positive**	• **HBV DNA: high†** >20 000 IU/mL • **ALT: elevated** Elevated is >30 IU/L men; >19 IU/L women • **HBeAg positive**	• **HBV DNA: low†** <2000 IU/mL • **ALT: normal** • **HBeAg negative** • **anti-HBeAg positive**	• **HBV DNA high†** >2000 IU/mL • **ALT: elevated** Elevated is >30 IU/L men; >19 IU/L women • **HBeAg negative** • **anti-HBeAg positive**
Treatment not required	**Refer to s100 community prescriber or specialist for consideration of treatment** Risk of progression to cirrhosis and HCC	**Treatment not required**	**Refer to s100 community prescriber or specialist for consideration of treatment** Risk of progression to cirrhosis and HCC

† Medicare covers HBV DNA testing once per year for patients not on treatment and 4 times per year for patient on treatment.

6 Provide ongoing monitoring

Regular monitoring is required to identify virological response, resistance and hepatitis flares, and to encourage adherence.

Indication	Monitoring specific to phase	PLUS, monitoring for all phases
HBeAg-positive chronic infection (Immune tolerance)	• Liver function tests (6-monthly) • HBV DNA (12-monthly)† • HBeAg and anti-HBe (6-12 monthly) • Assess for liver fibrosis (12-monthly)	• Periodic review of household contacts and sexual partners where appropriate • If indicated (see below): HCC surveillance
HBeAg-negative chronic infection (Immune control)	• Liver function tests (6-monthly) • HBV DNA (12-monthly)† • Assess for liver fibrosis (12-monthly)	
On treatment **HBeAg-negative chronic hepatitis (Immune escape)** **HBeAg-positive chronic hepatitis (Immune clearance)**	**3-monthly for the first year, then 6-monthly:** • Liver and renal function tests • HBV DNA† • Serum phosphate if on tenofovir disoproxil fumarate (TDF) **In addition:** • If HBeAg positive at baseline: HBeAg/anti-HBe (6-12 monthly) • If HBV DNA undetectable: HBsAg/ anti-HBs (12 monthly) • If cirrhotic: FBE and INR (3-monthly for the first year, then 6 monthly) Also assess adherence to treatment every review.	

HEPATOCELLULAR CARCINOMA SURVEILLANCE

6-monthly ultrasound with or without AFP is recommended for patients with CHB in these groups:

- People with cirrhosis
- Asian males > 40 years
- Sub-Saharan African people > 20 years
- Aboriginal and Torres Strait Islander people > 50 years
- Anyone with observed HBsAg loss with prior indications of HCC
- Māori and Pacific Islander males > 40 years
- Māori and Pacific Islander females > 50 years
- Asian females > 50 years
- Anyone with coinfection with hepatitis delta virus
- Anyone with a family history of HCC (first-degree relative)
- People from other racial groups, according to risk scores (e.g., PAGE-B)

ashm · Cancer Council · hepatitis australia · GESA · ASID · Australasian Hepatology Association

Case 1

- 32 M
- Routine screening
- No known family history

- Plt 67
- ALT 65
- AST 90
- Cr 107 umol/l

- Ultrasound: coarse, nodular liver with spleen 14 cm
- Fibroscan 15 kPa

- Treat or not treat?

Case 1

- APRI score
- FIB 4 score

Risk of disease progression

Male over >30 years

Raised ALT

Family history of hepatitis B related complications

Advanced fibrosis on fibroscan

Comorbidities (alcohol, diabetes, metabolic syndrome)

Coinfection (HDV,HCV, HIV)

Case 3

- 26F
- Diagnosed 4 yrs ago as part of antenatal screening
- 3 sisters pos but alive and well
- 4 children HBsAg neg
- Works as project assistant

- Well otherwise

- BMI 32
- ALT 26
- Plt 150

- US fatty liver
- Fibroscan 9.5kPa

- Treat ? Or not ?

Case 3

Fibroscan reading raised

?? Cause

Due to hepatitis B or other

? Coinfection

- Repeat bloods
- Role of viral load testing ??

Dose of antivirals

- Adults: Tenofovir DF 300 mg/day or Entecavir 0.5 mg per/day

- Children

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

[a] Children with body weight more than 30 kg should receive 10 mL (0.5 mg) of oral solution or one 0.5 mg tablet once daily.

Case RI

- 32F
- TDF Rx started in 2022 for raised ALT and family history
- Well otherwise
- Cr on testing 327 umol/L
- Weight 78 kg
- eGFR 27 ml>min
- What to advise:
  - Stop Rx
  - Dose reduce
  - Change to TAF
  - Repeat
- Why does she have renal impairment

Dose adjustments in renal impairment

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
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

Case 2

- 25 F
- No family history (liver cancer or cirrhosis)

- Plt 256
- ALT 25
- AST 16
- BMI 32

- US- fatty enlarged liver

- Fibroscan 5 kPa

- Treat or not Rx and why?

Chronic HBV Infection: Management of Pts With Renal Impairment

- All pts receiving TDF should undergo periodic monitoring of renal function, including phosphate levels[1]

Tenofovir Disoproxil Fumarate[3]	Tenofovir Alafenamide[4]
Reduce dose if CrCl < 50 mL/min	No dose reduction if CrCl ≥ 15 mL/min
No dose recommendation at CrCl < 10 mL/min without dialysis	Not recommended at CrCl < 15 mL/min

1. EASL. J Hepatol. 2017;67:370-398. 2. Entecavir [package insert]. 2017. 3. Tenofovir disoproxil fumarate [package insert]. 2017. 4. Tenofovir alafenamide [package insert]. 2017.

Case PA

- 45 M
- Started Rx 2019 for raised ALT
- Stopped after 2 months
- Restarted in 2022, stopped for 3 wks at intervals due to stock out
- Adherence issues
- What advise do you give them
- What are the risks of taking meds intermittently

Case PT

- 32 F
- Antenatal screening
- HBsAg pos at wk 28
- Previous 3 pregnancies (HBsAg neg)
- Started on TDF
- Stopped after one day due to vomiting and chills
- 3 children at home not tested
- What advise do you give her ??

Adverse effects of TDF in clinical trials

>10%

- Lethargy (11%)
- Diarrhoea (16%)
- Nausea (11%)
- Pain (12%)

1-10%

- Anorexia, dyspepsia
- Vomiting, abdominal pain
- Myalgia, peripheral neuropathy
- Depression
- Flatuence
- Rash
- Headache
- Neutropenia
- Increased transaminases

Managing common side effects

- Nausea and vomiting
- Pain
- Headache
- Fatigue

Listen

Acknowledge

Address

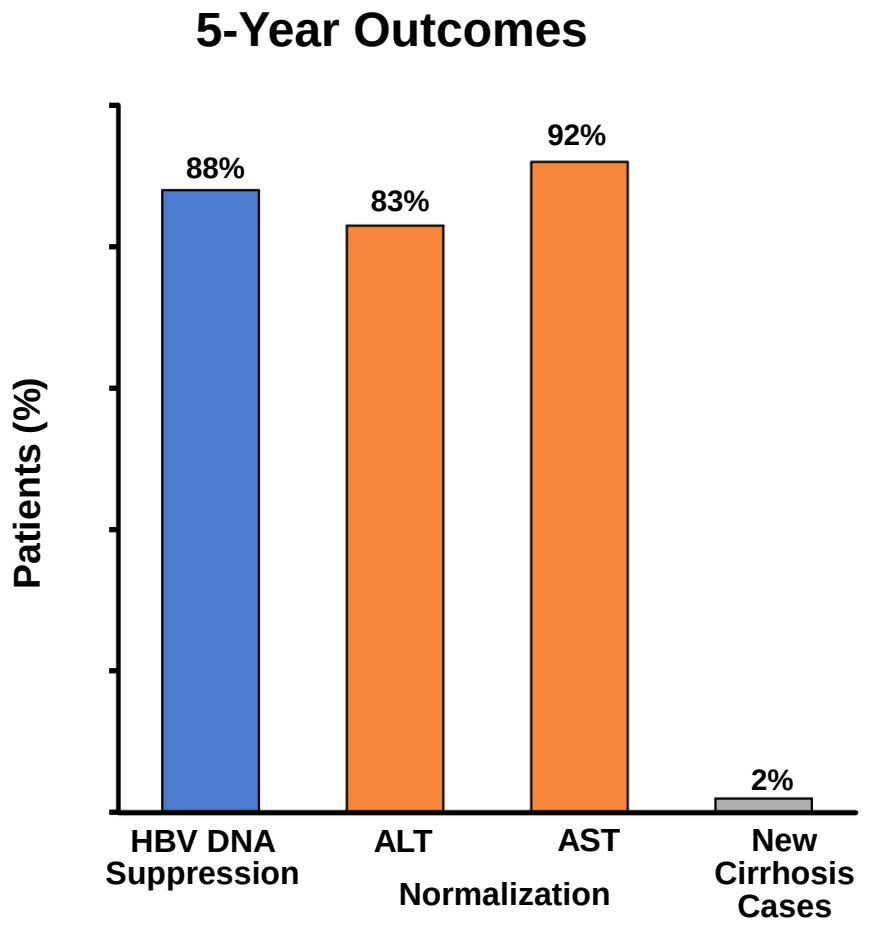
Early review

Alternatives to Rx ???

Remind pt of benefits of Rx

5-Year follow up of CHB patients on TDF Rx

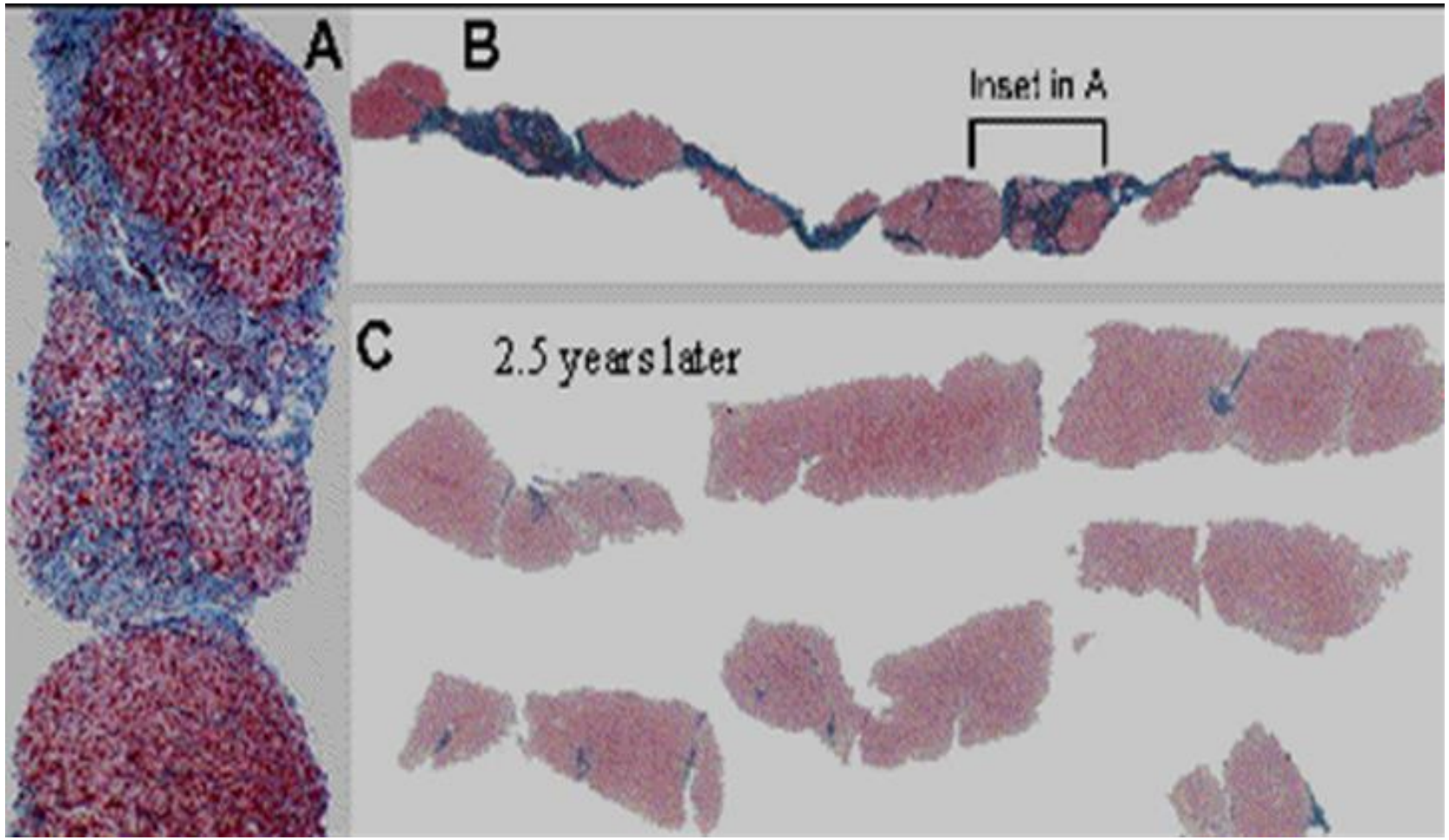
- Multicenter, 3-year retrospective, 2-year prospective study (n=357)
  - Males (69%)
  - Mean age: 48 years
  - Cirrhotics (n=7)
  - Follow-up: 65 months
- Cirrhosis progression
  - No progression among baseline cirrhotics
  - New cirrhosis (n=7)
- No development of HCC



Absence of cirrhosis defined by:
Liver biopsy (Metavir F0-F3); or transient elastography (≤12.5 kPa); or FibroTest® or FibroSure® (≤0.48 with APRI ≤1).

Ormeci N, et al. *Hepatol Int.* 2016;10(suppl 1):48. Abstract O-115.

Regression of cirrhosis after 2.5 years of antiviral therapy



Case 4

- 48 M
- New diagnosed on screening
- No known family history

- ALT 50
- Plt 170
- US normal
- Fibroscan 6.7kPa

- Rx or not Rx

- Counsel patients on pros and cons of Rx
  - Benefits- reduced disease progression, reduced liver cancer risk, reduced risk of transmission
  - Adherence- risk of flare and resistance
  - Need to monitor- response to Rx, renal impairment, liver cancer screening
- Consider stigma and discrimination
- Family screening

Case 4

- Rx started with TDF
- Review in 3 months for adherence and side effects
- 6 monthly follow up
  - Adherence
  - Liver cancer screening
- 12 monthly
  - Cr, ALT

Case 4

- Should he have a viral load ?
- What would we expect the result to be ??
- When to stop Rx
- HBsAg loss (ideally once a year), otherwise at 5 yrs

Monitoring on Rx

- Annual Cr, ALT (more frequent if cirrhosis or renal dysfunction)
- Liver cancer screening if indicated (6 m US)
- If available monitor for side effects and adherence at each visit
- Liver cancer screening
- Consider management of cirrhosis/varices/use of beta blockers/nutrition/reduce other liver stressors- alcohol

When to stop Rx

Cirrhosis – never

Non cirrhotic

- Ideal end point: HBsAg loss (<1% per year)
- Rx for 5 yr and test HBsAg, if neg, repeat after 12 m and stop if able to monitor

- Pregnant women after delivery
- Cancer Rx- 12 m after completion of chemotherapy

High rates of recurrence after Rx discontinuation (40-90% at 1 year)

Case 5

- 17 yo M
- Vertical transmission
- ALT 56, previously 52
- Plt 167
- Fibroscan 8 kPa
- Mother – liver failure and died in her 30’s
- Viral load > log 10 8
- HDV negative
- Rx or not Rx ??

When is viral load required

- Ideally- in all patients on a regular basis (annually) but cost and access prohibitive

- Consider in:
  - When results are likely to support Rx decisions
  - Younger patients with other likely causes of ALT rise
  - Pregnant women

- If viral load ND - no Rx required
- If high viral load – increased risk of disease progression
- Viral load in PMTCT
- Viral load in monitoring response to Rx
- Viral load in monitoring adherence
- Viral load in resistance

Case 5

- 36 F
- HepB dx based on outreach screening
- 2 children aged 7 and 11 – not tested
- 3 brothers (30's) and father (50's) (all died from hepatitis B related complications)

- ALT 27
- Plt 170
- Cr 87

- Ultrasound severe steatosis
- Fibroscan 28 kPa

- Rx or not Rx

Tenofovir alafenamide (TAF)

- TAF is a nucleotide reverse transcriptase inhibitor, and a phosphonamidate prodrug of tenofovir
- Compared with TDF, TAF is a more targeted form of tenofovir that has demonstrated high antiviral efficacy at a dose that is 10 times lower than TDF.
- Improved renal and bone safety profile
- TAF as a lipophilic cell-permeant compound enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3 and is converted to tenofovir diphosphate
- Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain-termination

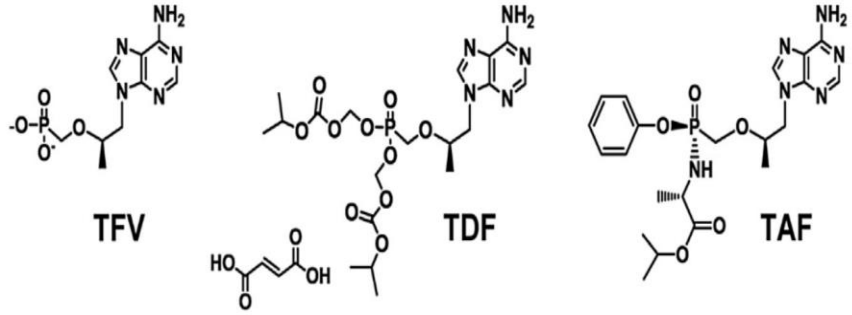


Fig. 1. Structures of acyclic nucleoside phosphonate tenofovir (TFV) and its lipophilic prodrugs tenofovir disoproxil administered as its fumarate salt (TDF) and tenofovir alafenamide (TAF).

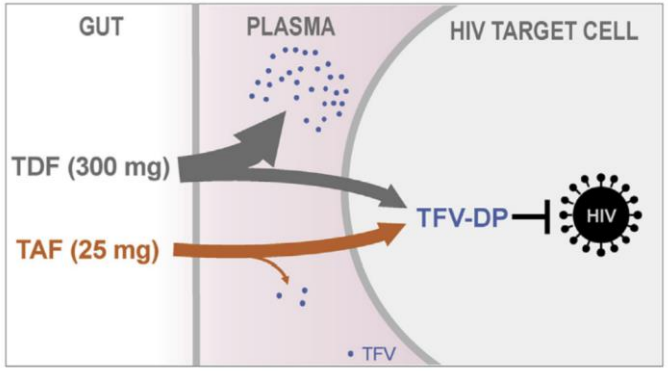
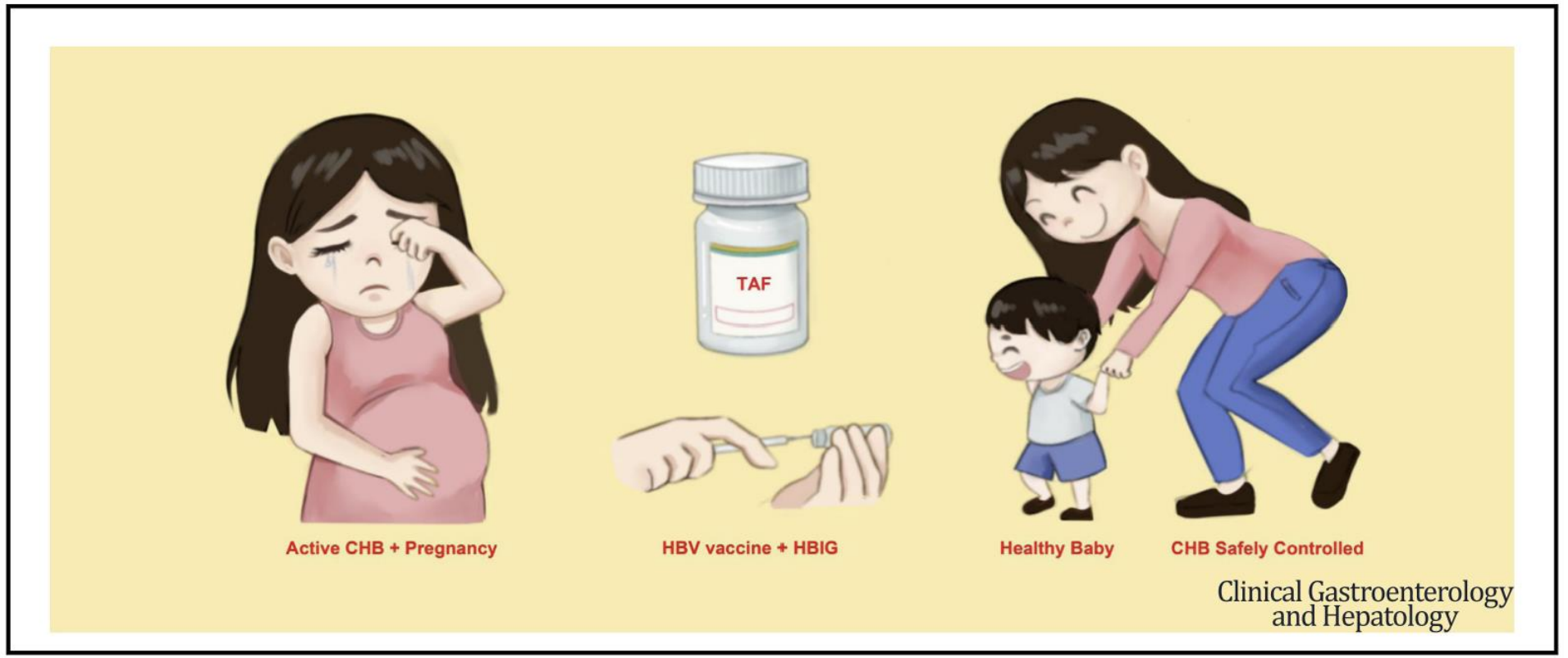


Fig. 3. Comparison of the efficiency of HIV-target cell delivery following oral administration of tenofovir prodrugs. Oral administration of TAF at 25 mg, 1/10th the molar equivalents of TFV present in 300 mg TDF, results in 90% lower systemic levels of TFV while maintaining intracellular levels of the pharmacologically active metabolite TFV-DP in HIV-target cells.

Clinical Gastroenterology and Hepatology 2022;20:2826–2837

Tenofovir Alafenamide for Pregnant Chinese Women With Active Chronic Hepatitis B: A Multicenter Prospective Study



Monitoring patients NOT on Rx

- Clinical review
  - Reassess risk factors
- Labs
  - Recalculate APRI and FIB 4 every year
  - ALT – if raised (on 2 occasions)- Rx
  - Male >30 IU/ml
  - Femaile >19 IU/ml
- How often:
- 6-12 monthly ALT (Rx if raised)
- More often in pts at risk of disease progression
- Liver cancer screening

Liver cancer screening

HOW

- 6 monthly US +/-AFP
- CT (triple phase) if new >1 cm liver lesion in a patient with hepatitis B

WHO to screen

- All cirrhosis
- All with family history of HCC
- Male over 40 years
- All coinfected with hepatitis D
- Female over 50 years

Hepatitis D testing

- To date >1200 sample collected as research but no ongoing support for routine testing
- Over 40% positive
- Routine testing ideal with HDV Ab and if positive HDV viral load
- Rx now available
- Leads to more aggressive disease –HCC and advanced cancer

Key take home messages

- All patients should be considered for Rx
- Is this patient cirrhotic ??
- Is this patient at risk of disease progression
- Does this patient need liver cancer screening
- COUNSELLING
- ADHERENCE

- Plt
- ALT (6m)
- AST
- Cr (baseline and annually on Rx)

- US (6m)
- Fibroscan (2yrs)
- Viral load (consider if it will help!!)

Challenges of program

- Logistics pathway: meds, lab supplies, drugs
- Medical records:
- Data capture:
- Adherence:
- Staffing: Medical and nursing
- Outer islands: Test and Rx and evolution

- HDV
- HCC

- Expansion expected: Consider alternative models of delivery of care. Role of nurse assistants on Tarawa to increase adherence, support clinics, admin assistants ?

Staging liver disease

- Staging relates to amount of fibrosis
- Staging informs:
  - Decision to start treatment
  - Monitoring for complications
  - Determining the prognosis
- Cumulative 5-year survival in pts with decompensated cirrhosis (bleeding varices, ascites, encephalopathy, jaundice) is 35%
- Staging predicts progress to decompensation (a clinical syndrome)

Tests of liver fibrosis

Invasive tests

- Liver biopsy – Gold standard

Non-invasive tests

- Liver tests
- Platelets
- APRI
- FIB4
- Ultrasound
- Transient Elastography

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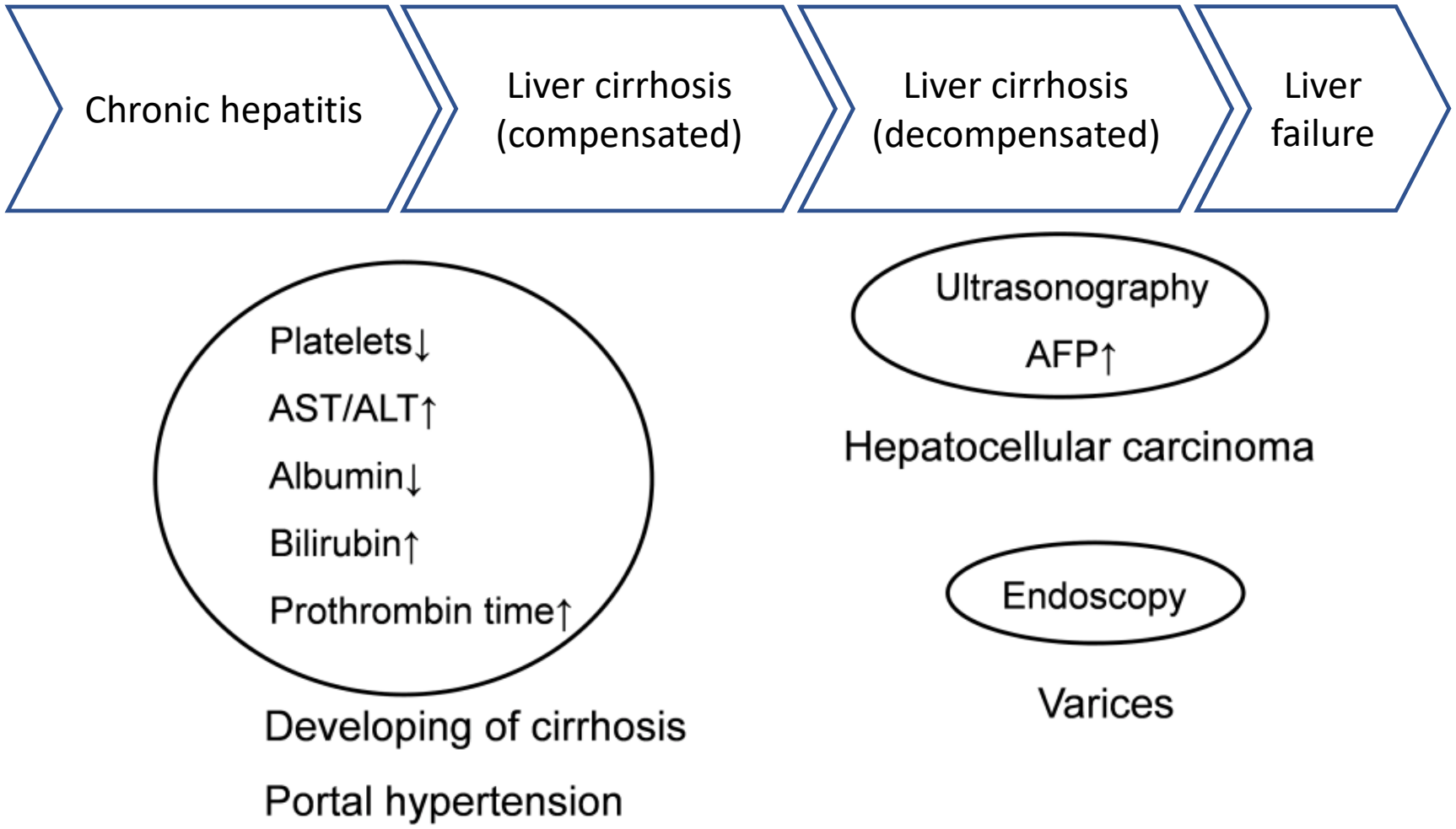
Assessing the severity (staging) of liver disease



History and clinical assessment: Complications of cirrhosis (spider naevi, cirrhotic liver, splenomegaly, varices, ascites)

Non-invasive tests (NIT) based on bloods or serum indices

APRI = * (AST/ULN) x 100) / platelet count (10^9/L)

FIB-4 = (age (yr) x AST (IU/L)) / (platelet count (10^9/L x [ALT (IU/L)$^{1/2}$])

WHO Guidelines, 2015

AST Platelet Ratio Index (APRI)

$$\textbf{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

- AST upper limit of normal: Use 40 IU/L if none specified
- Platelet count: expressed in terms of X1000/microlitre

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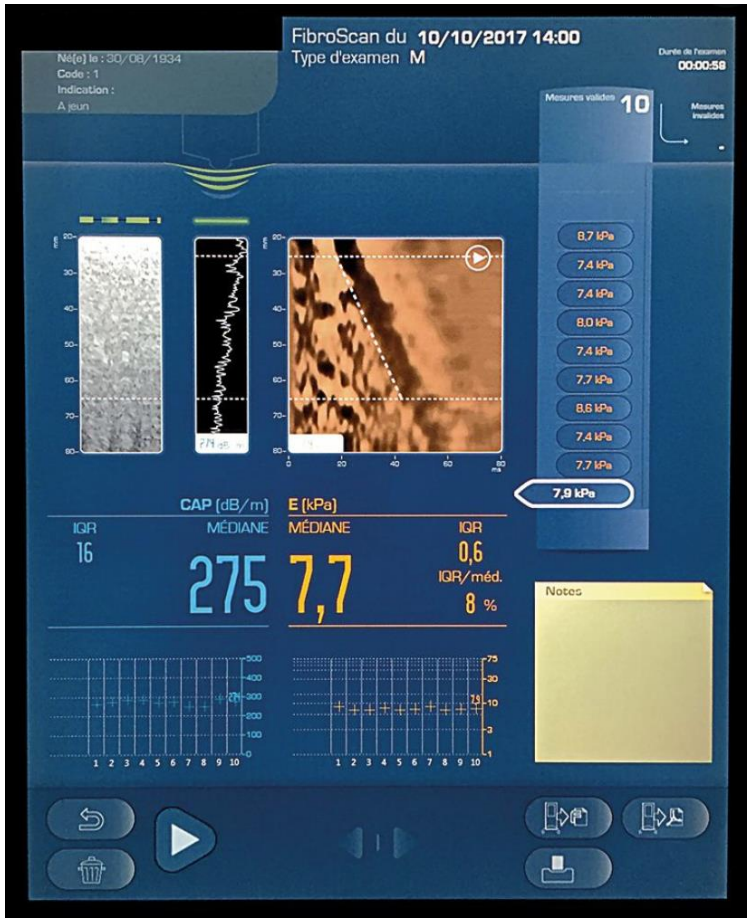
FIB-4

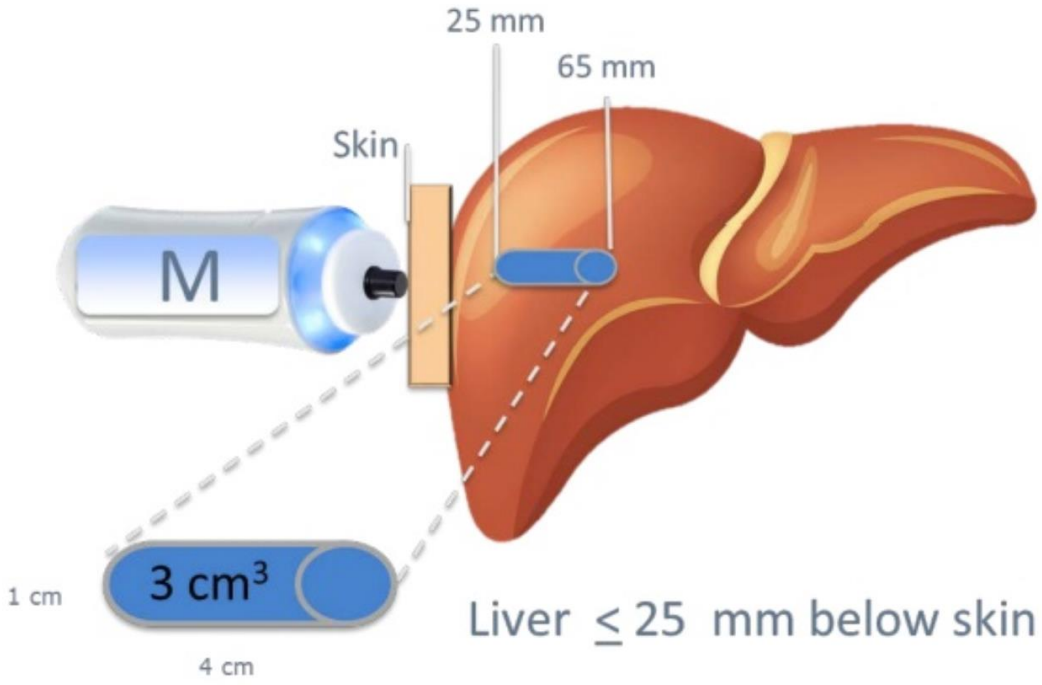
$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

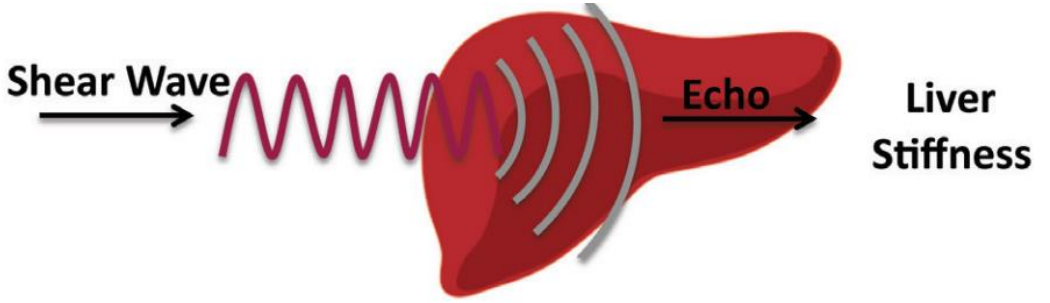
- AST/ALT upper limit of normal: Use 40 IU/L if none specified
- Platelet count: expressed in terms of X1000/microlitre
- Calculation needs a calculator, a phone App or an online tool

Transient Elastography (Fibroscan®)

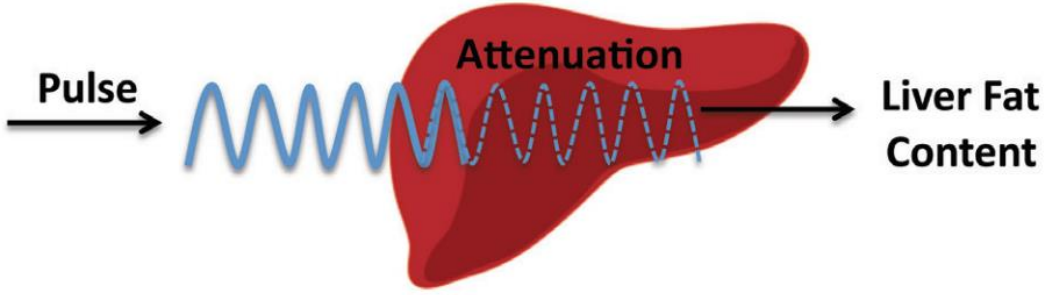


Mechanism of Transient Elastography (Fibroscan®)





Controlled Attenuation Parameter (CAP):



Cirrhosis

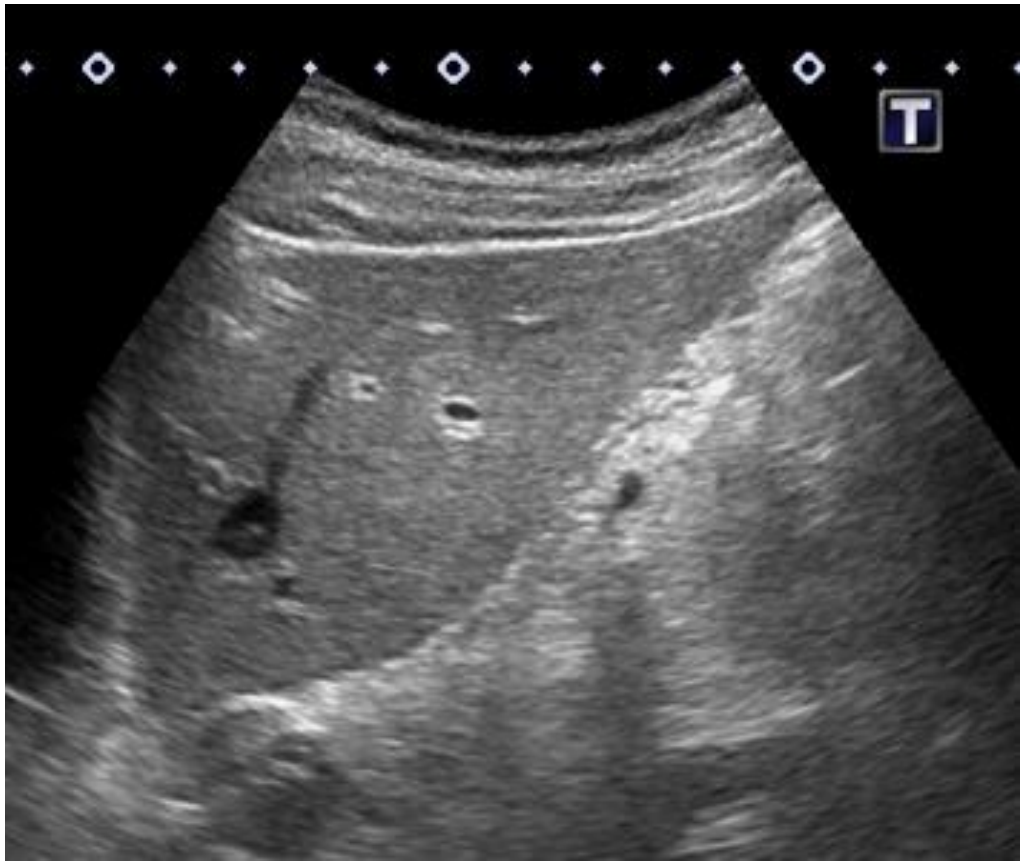
An advanced stage of liver disease characterized by

liver necrosis and regeneration with subsequent
extensive hepatic fibrosis resulting in
alteration of liver architecture
disrupted hepatic circulation
nodule formation - both microscopic and then macroscopic

Abdominal ultrasound

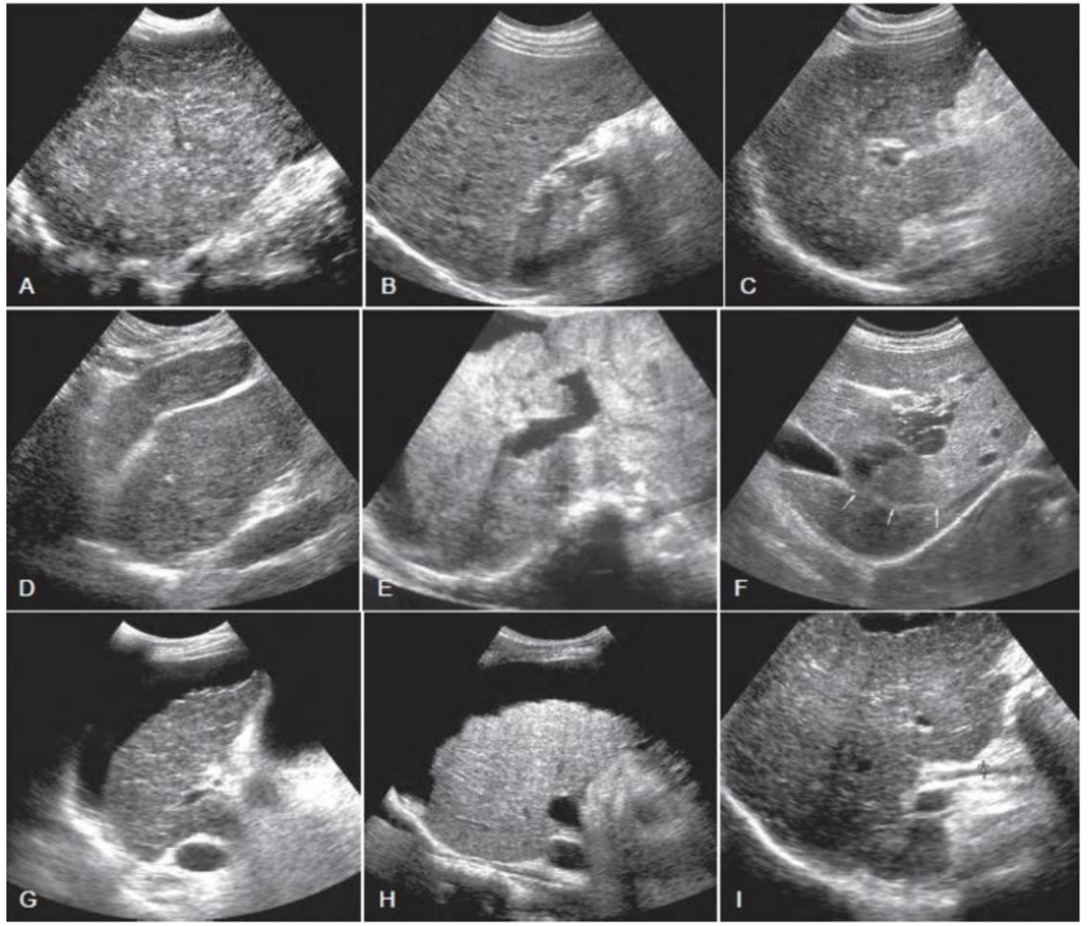
- Most widely used and available
- Can differentiate cirrhosis versus no cirrhosis
- Identify the features of portal hypertension, an indirect marker of cirrhosis
- However, cannot reliably differentiate between F0-F3
- Even for cirrhosis, sensitivity/specificity low
- Operator/machine dependent

Normal ultrasound



Abdominal ultrasound: Markers of cirrhosis

- Small shrunken liver
- Nodular surface with irregular margins
- Coarse echotexture
- Features of portal hypertension
  - Enlarged spleen (>11 cm)
  - Dilated portal vein (diameter >12 mm)
  - Presence of venous collaterals
- Presence of complications
  - Ascites



Assessing the degree of liver fibrosis: Non invasive tests (NIT)

	Fibrosis stages assessed	Cut-off values for the detection of fibrosis	
		Cirrhosis (METAVIR F4)	Significant fibrosis (METAVIR ≥ F2)
APRI	≥ F2, F4	**High cut-off 2.0**	**High cut-off 1.5**
FIB-4	≥ F3	High cut-off 3.25	
Fibroscan®	≥ F2, F3, F4	> 11-14 kPa	> 7-8.5 kPa

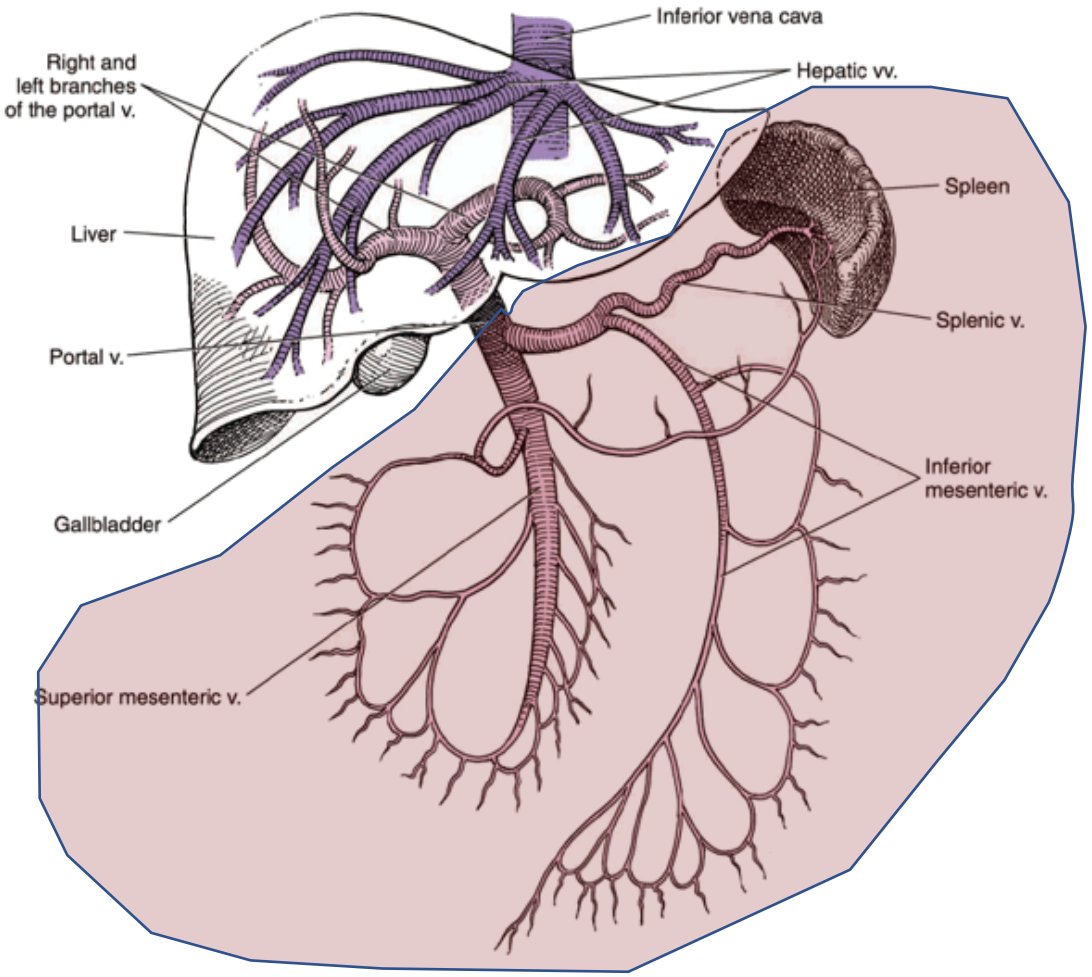
- APRI = [(AST(IU/L)/ AST_ULN(IU/L)) x 100] / platelet count (10^9/L)

  ULN signifies the upper limit of normal for AST in the laboratory where these investigations were undertaken

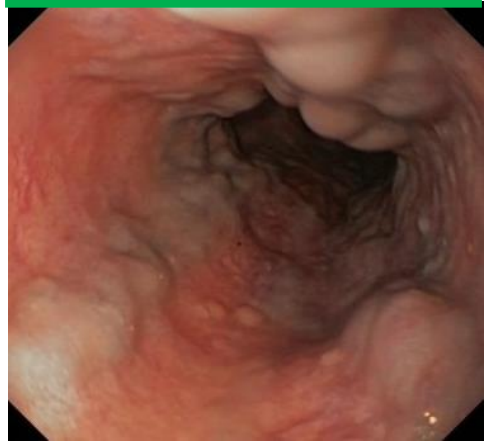
- FIB-4 = age(yr) x AST(IU/L)/platelet count(10^9/L) x [ALT(IU/L)$^{1/2}$]

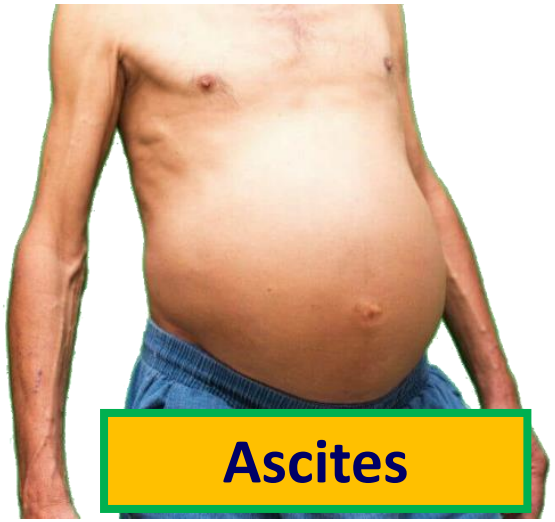
WHO Guidelines, 2015

Features of portal hypertension



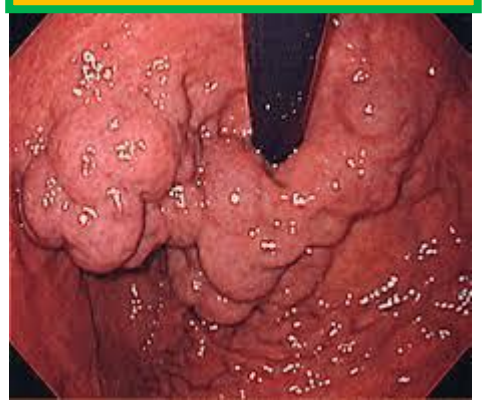
Esophageal Vx



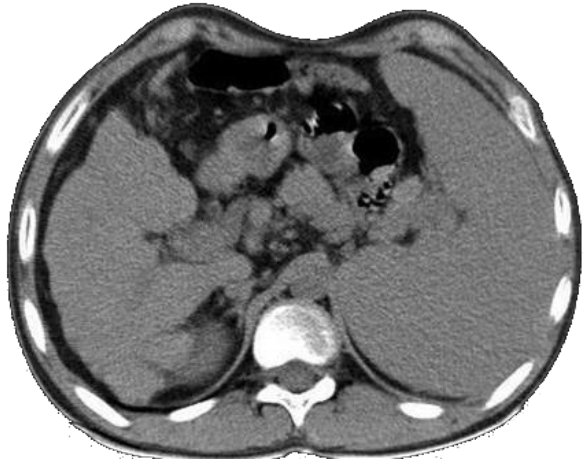


Ascites

Gastric Vx



Splenomegaly



Fibroscan readings and portal hypertension

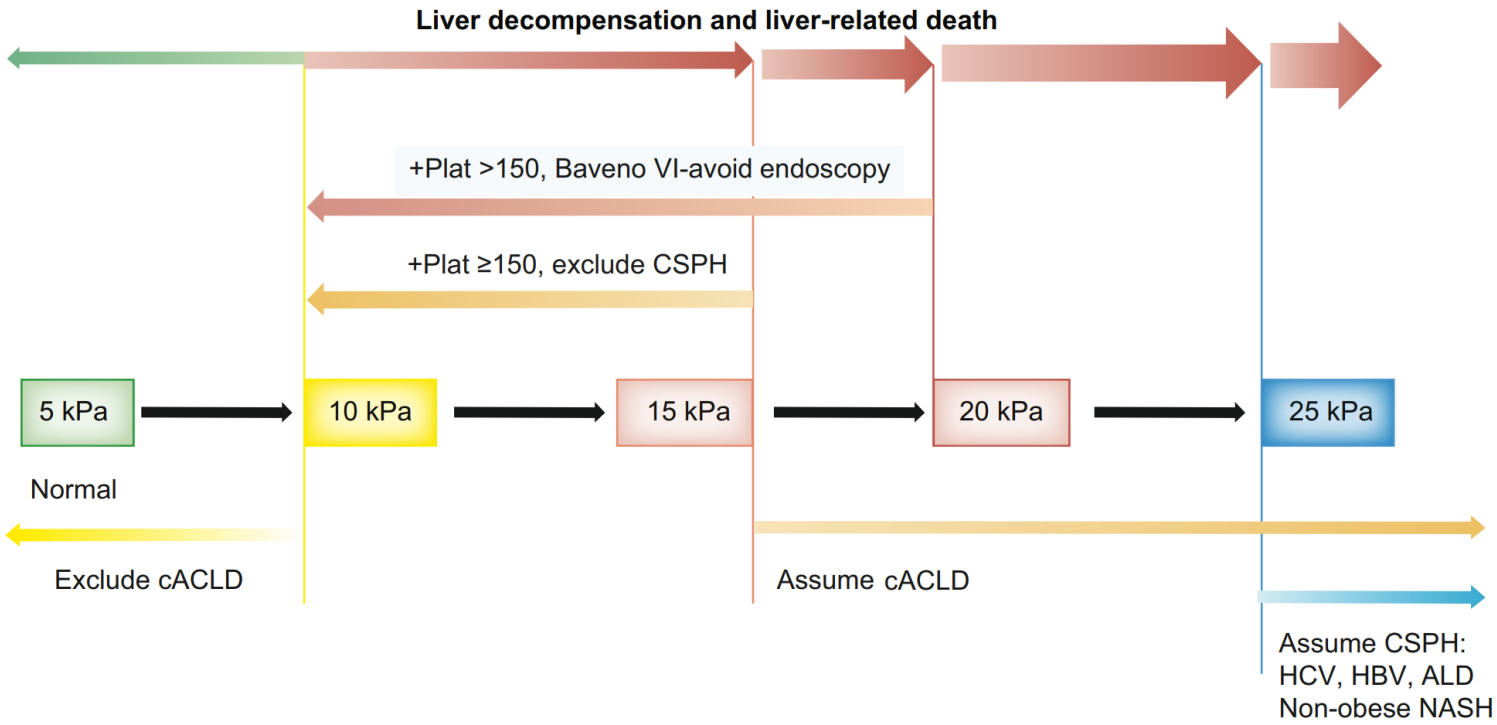


Fig. 1. Algorithm for the non-invasive determination of cACLD and CSPH. ALD, alcohol-related liver disease; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; NASH, non-alcoholic steatohepatitis.

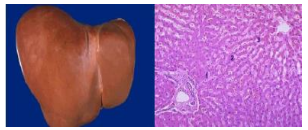
aasld.org/practice-guide...

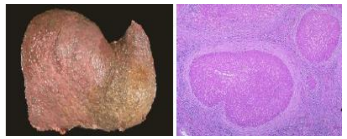
LS 15-20 kPa	LS 20-25 kPa	LS >25 kPa	Varices or Portosystemic collaterals or hepatofugal flow or HVPG≥10
Plt <110	Plt <150	ANY Plt	
= Clinically Significant Portal Hypertension (CSPH)			
→Treat with NSBB, preferably Carvedilol			

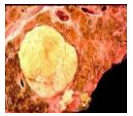
Natural History of End-Stage Liver Disease (ESLD)

Increasing liver fibrosis

Development of HCC







Chronic liver disease → Compensated cirrhosis → (5-7% pa) Decompensated cirrhosis → Death

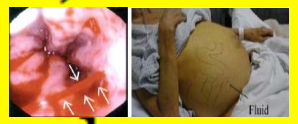
- Alcohol
- Hepatitis C or B virus
- NASH
- Cholestatic
- Autoimmune

Predominantly due to: (a) Hepatic Synthetic Failure (b) Portal Hypertension and (c) Portosystemic shunting

- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice

Decompensation

- Ascites (HRS, SBP)



- Encephalopathy
- Bleeding varices
- Coagulopathy