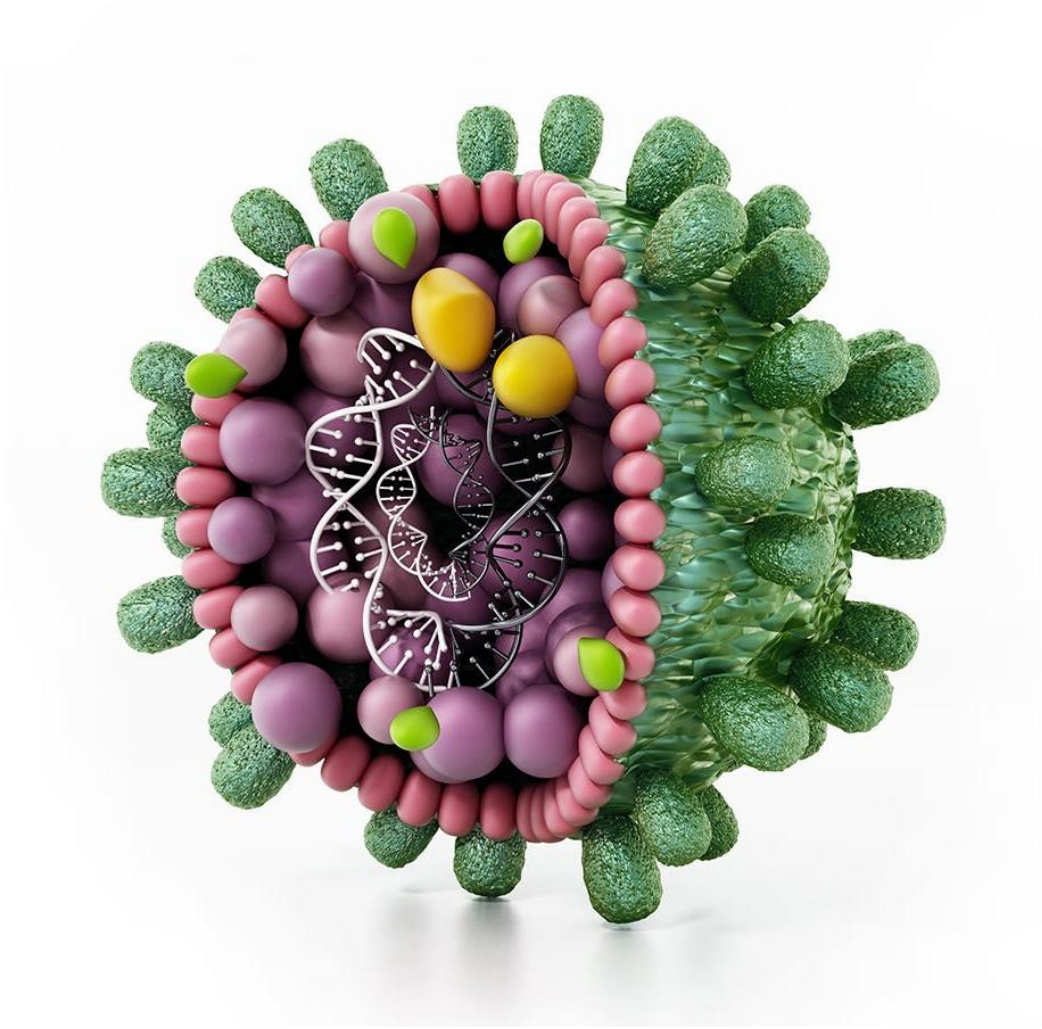
Hepatitis B

Dr Elizabeth Gatley

Moderator: Professor Spearman



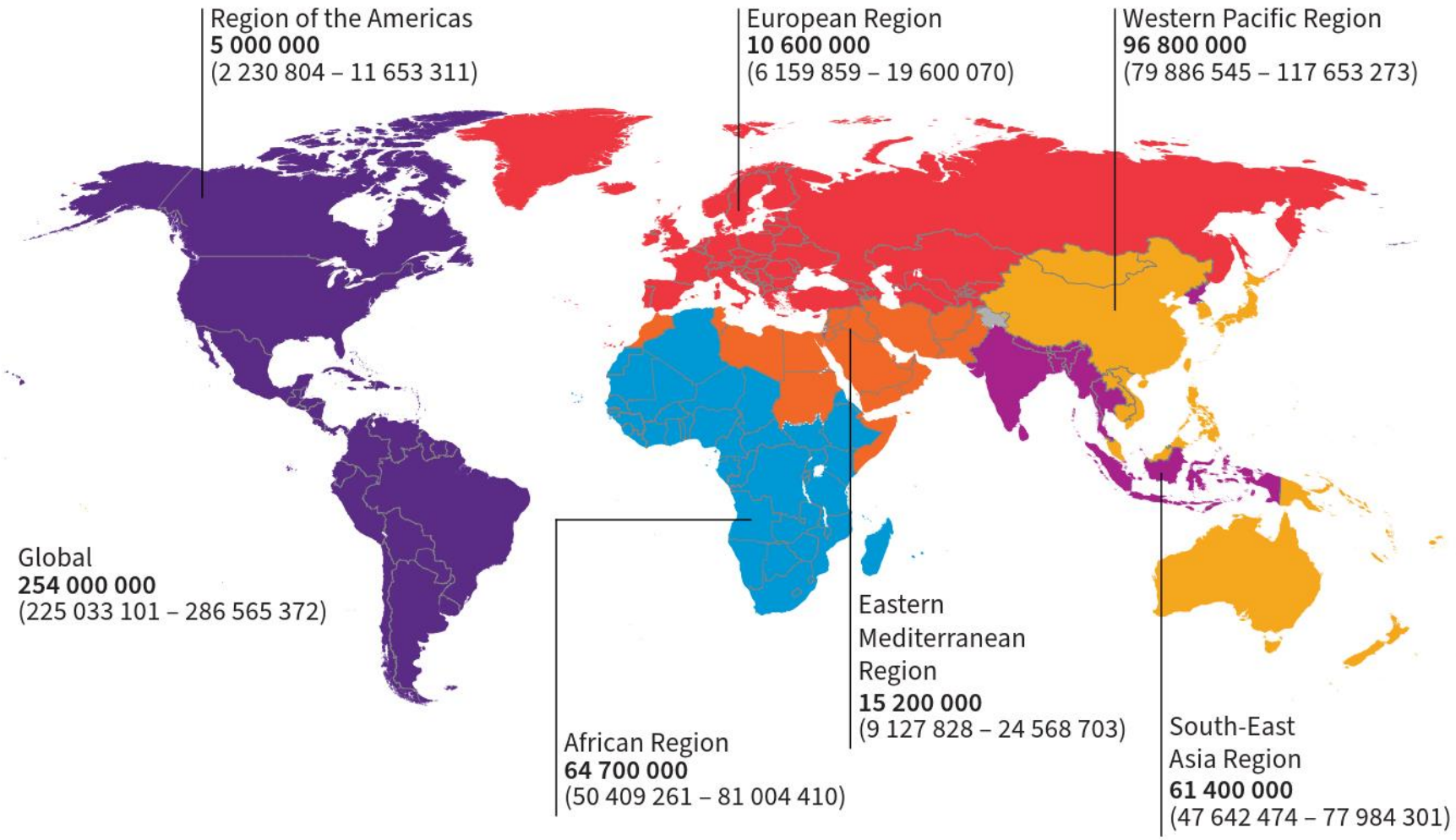
Project ECHO
Gastroenterology Foundation of sub Saharan Africa

G-ECHO
GI HEPATOLOGY ECHO OF SUB-SAHARAN AFRICA
ESTABLISHED 2020

Outline

- Current Epidemiology
- Transmission and Virology
- Serological markers
- Natural history of infection
- Extrahepatic manifestations
- Treatment guidelines
- Coinfections
- PMTCT
- Looking to the future

Global Prevalence of Chronic HBV infection



- Up to 95% of those with HBV and/or HCV are unaware of their infection
- HBV is entirely vaccine preventable (1982)

- Seroprevalence varies depending on sex, ethnicity and rural vs urban areas
- Prevalence >8% considered endemic – usually established in childhood

- Concerns of increasing infections and deaths secondary to complications
- 15-40% risk of cirrhosis, liver failure or HCC
- 15-25% risk of dying from HBV related liver disease

Sub-Saharan Africa and South Africa

- In Africa 64 million people are estimated to have chronic hepatitis B
- Approximately 2.5 million in South Africa

- South African prevalence prior to EPI varied from 0.3% - 15%
- 1995 Hepatitis B vaccine was introduced into the vaccination schedule in SA

  BUT
  - No catch-up vaccination program
  - Co-infection with HIV results in a more aggressive disease course BUT excellent antivirals available
  - Timing of infection: largely perinatal with a much higher risk of developing chronic hepatitis B
- Current prevalence of 3.5% has been largely static over more than a decade reflecting the need for PMTCT including birth dose vaccine for further impact
- Perinatal infection results in 25% increased risk of death from cirrhosis or HCC if male and 8% risk if female

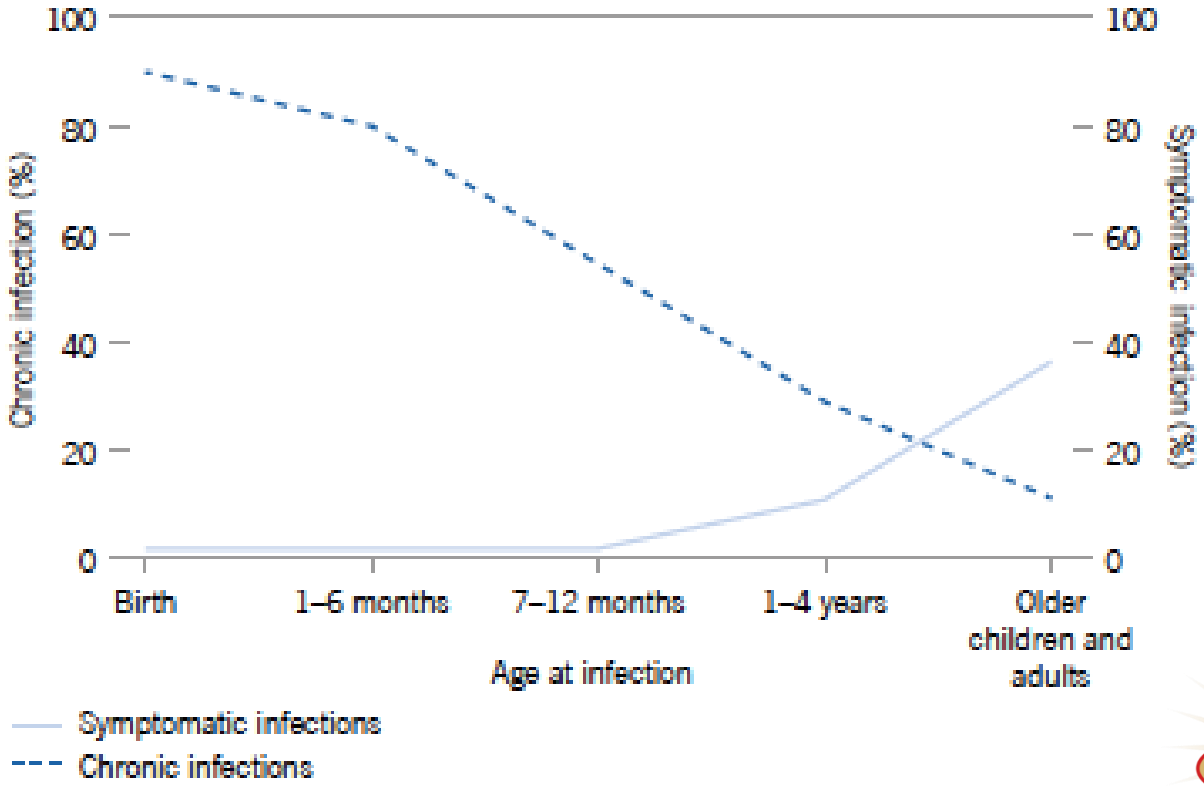
WHO Global Hepatitis strategy

- To eliminate viral hepatitis as a global health threat by 2030
- **TARGETS**
- 90% reduction in new cases of chronic Hep B and C
- 65% reduction in mortality secondary to HBV and HCV
- Requires: 80% of treatment-eligible people to be on treatment for both HBV and HCV

Transmission

- Highly contagious (100x more than HIV)
- Can survive in dried blood for up to 1 week
- Transmission:
    - **Mother-to-child (vertical)**
    - **Close household contacts (horizontal/familial)**
    - Sexual contacts
    - Percutaneous exposure (IDU, Needle stick)
- **Perinatal transmission: conversion to chronic HepB up to 90%**
- **Acquisition 1 – 5 yrs old: 20 – 50 % conversion to chronic HepB**
- Adult acquisition: < 5% develop chronic HepB

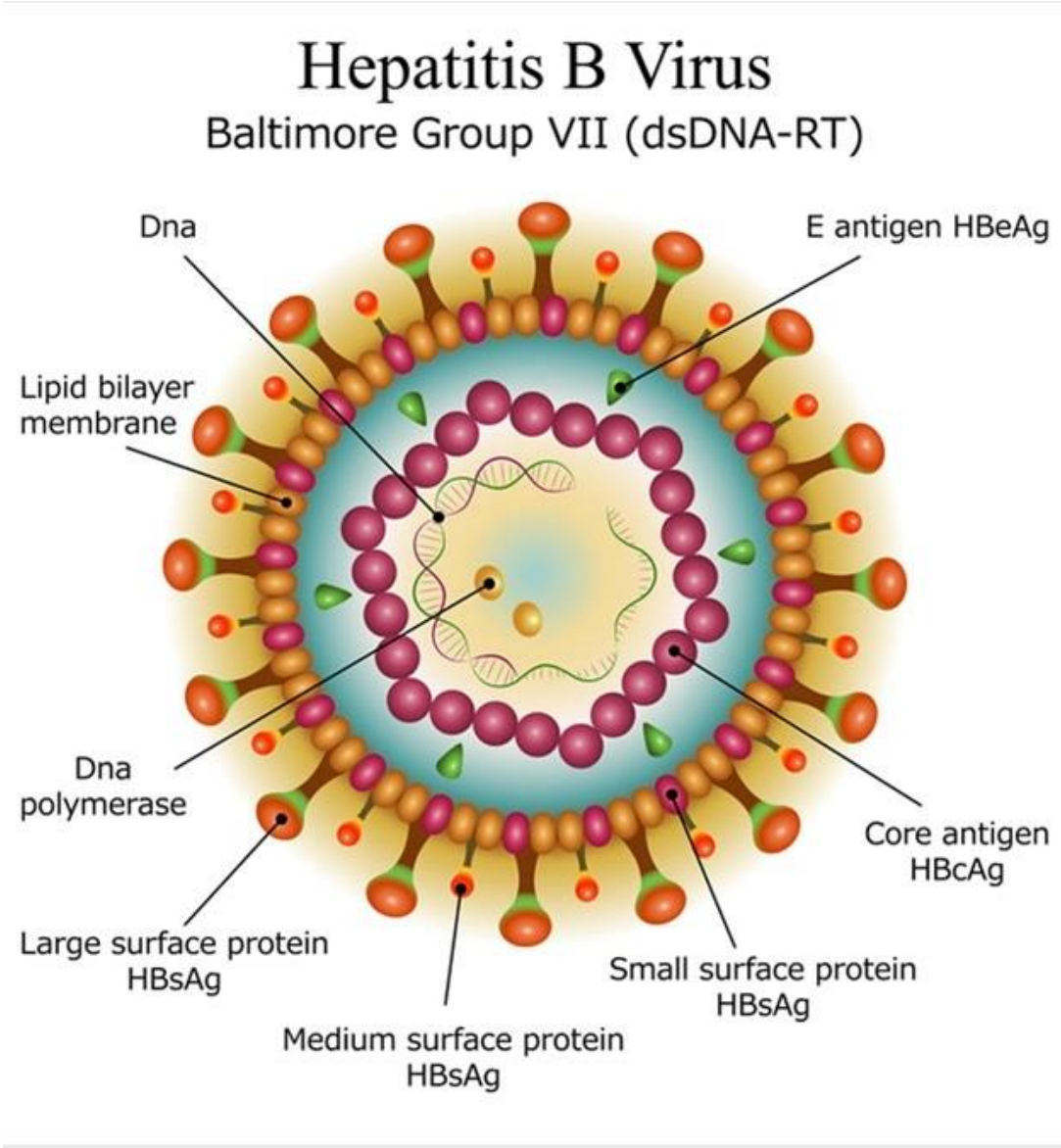
FIGURE 2.1 Outcome of hepatitis B infection by age at infection

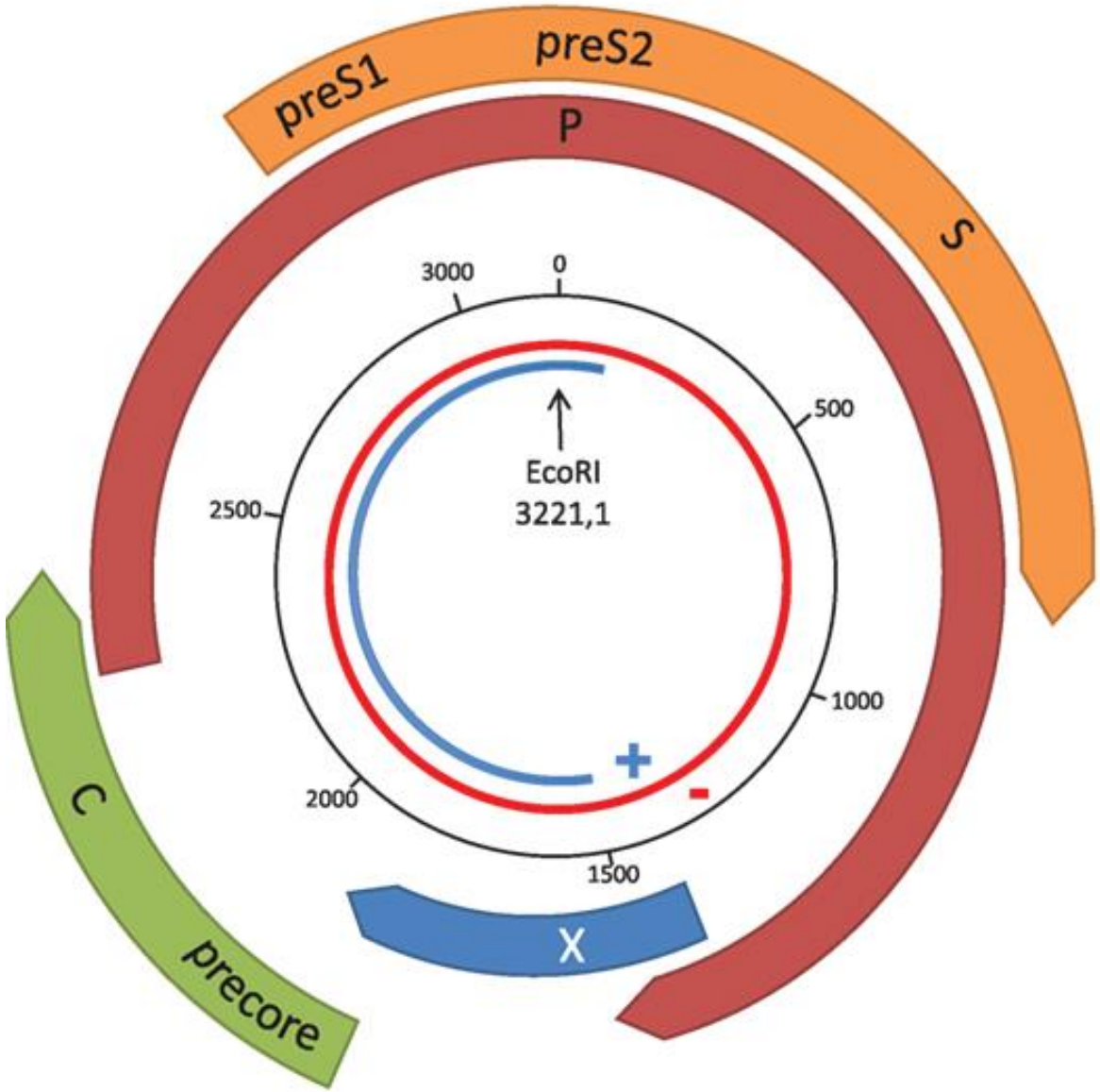


World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection [Internet]. Geneva: World Health Organization; 2024 [cited 2025 Feb 1]. Available from: https://www.who.int/publications/i/item/9789240090903

The Virus

- Hepadnaviridae family
- Enveloped, partially double stranded **DNA virus**
- The DNA exists as relaxed circular DNA with 4 open reading frames for coding of proteins
- At least 10 genotypes (A to J)
- Replicates and assembles exclusively in hepatocytes
- Not directly hepatotoxic
- Liver injury secondary to immune response to infected cells
  - CHB largely due to T cell exhaustion
  - B-cell immune response is important in recovery from acute infection
- Considered an oncogenic virus





Gene S → HBs protein

- Outer envelope protein
- Non-infectious subviral HBsAg particles outnumber infectious virions by x100–10 000
- HBsAg promotes T cell exhaustion.
- *Immune/diagnostic escape mutants*

Gene P → Polymerase

4 domains, with 3 enzymatic activities:

- Terminal Protein (TP) domain: protein-priming function
- Non-conserved spacer domain (no enzymatic activity)
- Reverse Transcriptase domain: RNA-dependent DNA polymerase (RT) and DNA-dependent DNA polymerase
- RNase H domain: ribonuclease H activity
- *Drug resistance mutations*

Gene C → HBc/HBe proteins

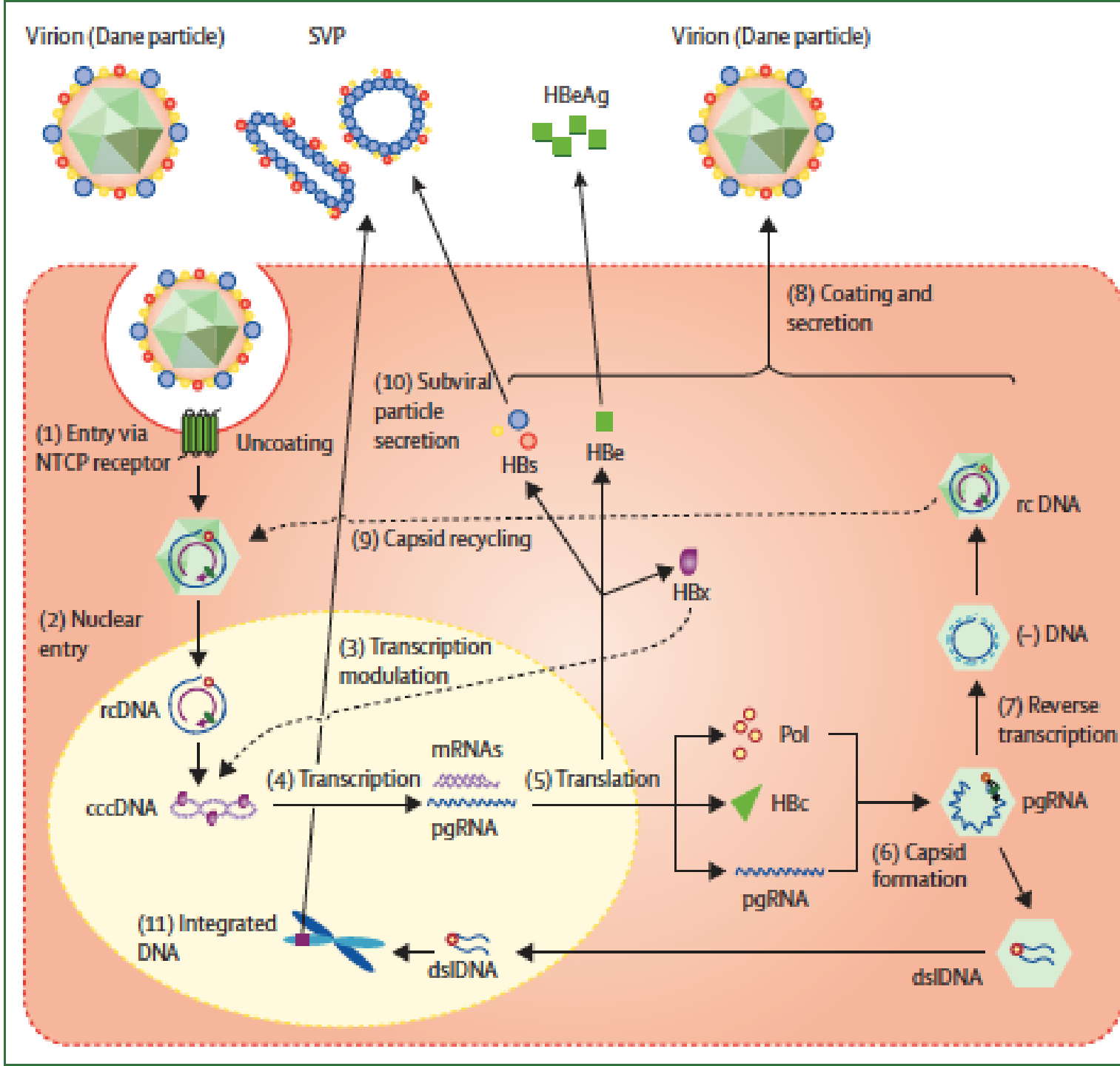
- HBc antigen: icosahedral nucleocapsid
- HBe antigen: immunoregulatory roles
    - viral persistence, suppresses anti-viral T cell responses against HBcAg by stimulating T-reg cells
    - drive pro-inflammatory T cell polarization during viral clearance
    - may induce immunologic tolerance *in utero*
- *Pre-core mutants truncates precore/core protein*
- *Core promoter mutants – associated with fulminant hepatitis*

Gene X → HBx protein

- HBx regulates viral replication and host functions eg. transcription, cell cycle progression, DNA damage repair, apoptosis
- *Truncation mutants associated with oncogenesis*

Lifecycle of HBV

- Enters via NTCP receptor
- rcDNA repaired to form cccDNA
- cccDNA forms a template for transcription for mRNA and pgRNA
- This is translated into viral proteins which can be packed to form new virions.
- Some capsids with rcDNA are recycled back to the nucleus to boost the pool of cccDNA
- The X protein modulates some of this processing.
- Note viral DNA is integrated into the host genome



Dusheiko G, Agarwal K, Maini MK. New Approaches to Chronic Hepatitis B. N Engl J Med. 2023;388(1):55-69

HBV serological Markers

- **HBsAg**
  - Marker of infection
  - First serological marker to appear
  - Surrogate for transcriptionally active cccDNA
  - Chronic if present >6 months
- **HbeAg**
  - Marker of active viral replication
  - Absent in some viral mutations

- **Anti-HBs (HBsAb)**
  - Recovery and/or immunity to HBV
  - Detectable with vaccination conferred immunity
- **Anti-Hbe (HBeAb)**
  - HBeAg to Ab seroconversion with halting of replication
  - Present in HBeAg – CHB with active replication due to mutant strains
- **Anti-HBc total (HBcAb total) = IgM +IgG**
  - *IgM anti HBc* – acute infection or reactivation
  - *IgG anti HBc* – Most sensitive marker of past infection. (note: HBsAb may be undetectable if infection acquired in childhood)

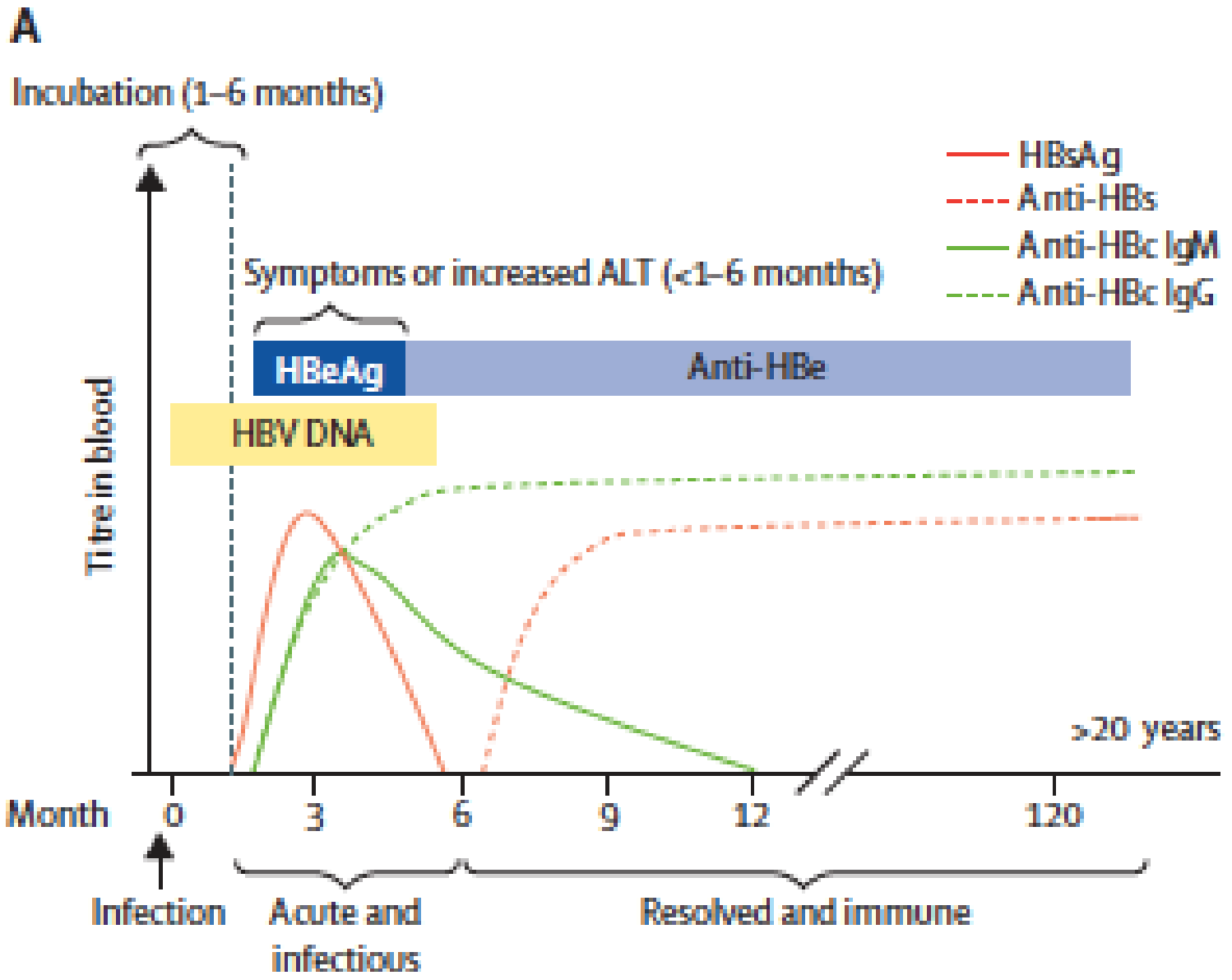
Acute Hepatitis B (adolescent/adult)

- Incubation of 4 – 12 weeks
- 70% asymptomatic
- Typical viral prodrome (anorexia, malaise, myalgia)
- Many may clear the infection without progression to significant liver impairment
- Some develop jaundice and more significant symptoms (serum sickness)
- 0.1 - 1% present with fulminant hepatitis and liver failure (sAg may be negative)
- Diagnosis made with HBsAg + and HBcIgM + (note may also be present in a flare)
- >95% of adults should achieve clearance with only supportive treatment

Acute Hepatitis B Treatment

- Largely supportive:
  - Bed rest
  - High caloric diet
  - Avoidance of hepatotoxins
- Initiation of antiviral therapy:
  - Severe acute infection: coagulopathy (INR > 1.5) or protracted course (>4 weeks of severe jaundice and symptoms)
  - Any signs of liver failure
  - Treatment with monotherapy NA (LAM, TDT/TAF or ETV)
- Fulminant liver failure
  - ICU, low protein diet, antiviral therapy, possible prophylactic antibiotics, control bleeding
  - May need consideration for urgent liver transplant

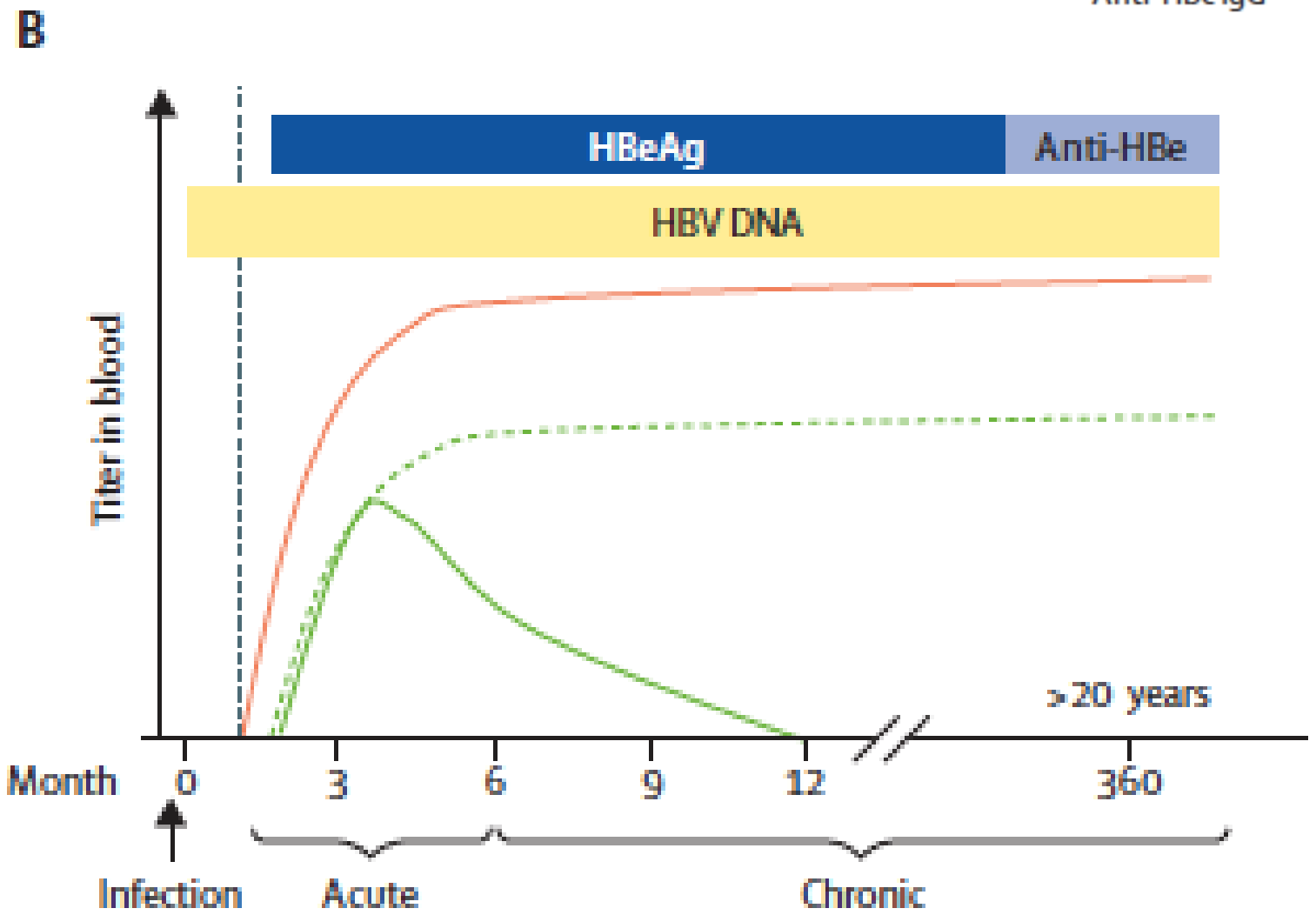
Acute Hepatitis B



Jeng WJ, Papatheodoridis GV, Lok ASF. Hepatitis B. Lancet. 2023;401(10381):1039-52

Chronic Hepatitis B

Persistence of HBsAg > 6 months



Jeng WJ, Papatheodoridis GV, Lok ASF. Hepatitis B. Lancet. 2023;401(10381):1039-52

New nomenclature for chronic phases

- The natural history of chronic HBV infection has been schematically divided into five phases

Chronic hepatitis B / Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

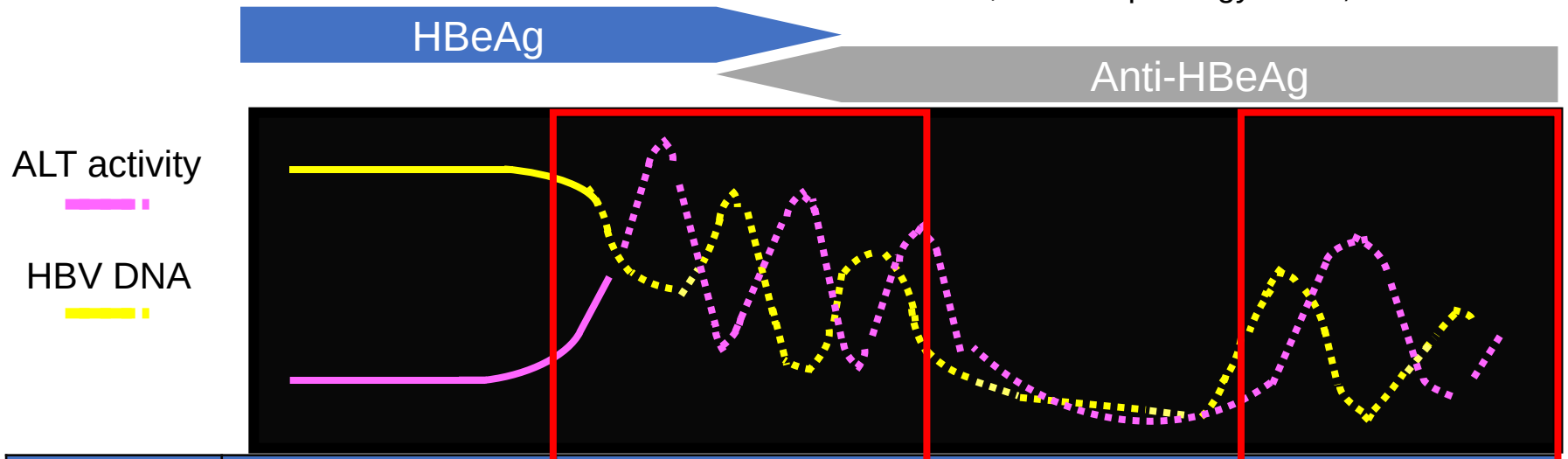
*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persisitently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

EASL™ The Home of Hepatology

Phases of Chronic HBV Infection

Natural history dynamic and complex. Phases have variable duration and are not necessarily sequential. All phases potentially require Rx.

Yim HJ, et al. Hepatology. 2006;43:S173-S181



Phase	Immune Tolerant	Immune Clearance	Immune Control	Immune Escape
	HBeAg pos Chronic HBV Infection	HBeAg pos Chronic HBV Hepatitis	HBeAg neg Chronic HBV infection	HBeAg neg Chronic HBV Hepatitis
Liver	Minimal inflammation and fibrosis	Chronic active inflammation	Mild hepatitis and minimal fibrosis	Active inflammation and progressive fibrosis

Phase 5: Occult Hepatitis B

- **HBsAg negative, HBc total +, HBsAb +/-**

- Low-level HBV replication may persist with detectable HBV DNA **in the liver**
- HBV DNA is not detectable in the serum or <200 IU/ml
- HBsAg loss before the onset of cirrhosis associated with improvement of the outcome with reduced risk of cirrhosis, decompensation and HCC
- If cirrhosis has developed - at risk of HCC and need surveillance
- **NOTE: Immunosuppression may lead to HBV reactivation – particularly B cell depleting therapies**

Table 2. Immunological markers, DNA levels and ALT in HBV infection

	Acute hepatitis B	Recovery from acute hepatitis B	Immune tolerant state	Chronic HBV disease		Inactive HBsAg carrier state	Occult hepatitis B
				HBeAg positive	HBeAg negative		
HBsAg	✓		✓	✓	✓	✓	
Anti-HBs		✓					
Anti-HBc IgM	✓						
Anti-HBc IgG	✓	✓	✓	✓	✓	✓	✓
HBeAg	✓		✓	✓			
Anti-HBe		✓			✓	✓	
HBV DNA (IU/ml)	High	Negative	>20 000 IU/ml	>20 000 IU/ml	>2 000 IU/ml	<2 000 IU/ml	<200 IU/ml
ALT	Elevated	Normal	Normal	Elevated	Elevated	Normal	Normal

HBsAg = hepatitis B surface antigen; Anti-HBs = detection of hepatitis B surface antibody; Anti-HBc = detection of hepatitis B core antibody; IgM = immunoglobulin M; IgG = immunoglobulin G; HBeAg = hepatitis B 'e' antigen; Anti-HBe = detection of hepatitis B 'e' antibody; HBV DNA = hepatitis B virus DNA; ALT = alanine transaminase.

Extrahepatic manifestations associated with HBV infection

Acute HBV infection

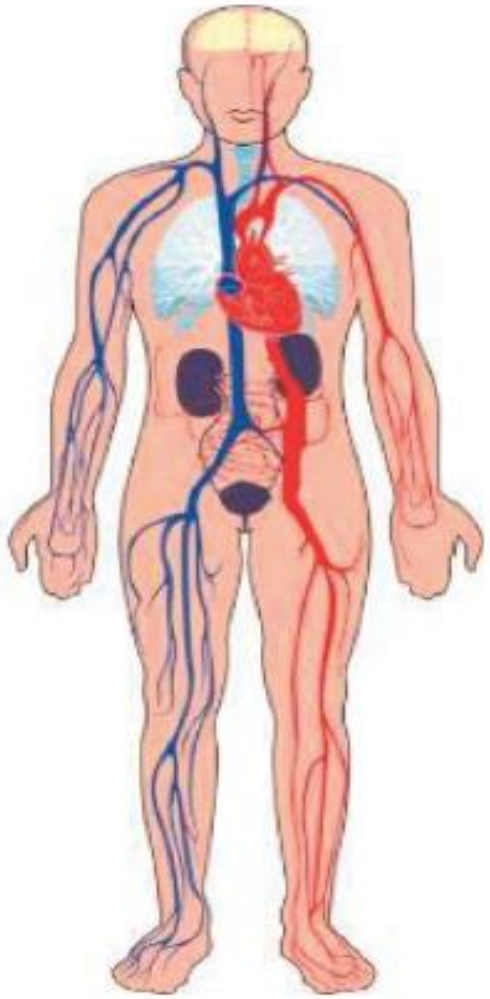
Systemic
- Flu-like syndrome
- Serum sickness
- Polyarteritis nodosa *
- Cryoglobulinemia *

Rheumatological
- Polyarticular joint pain
- Polyarticular arthritis

Skin
- Papular acrodermatitis of childhood
- Acute urticarial
- Leukocytoclastic vasculitis

Renal
- Membranous glomerulonephritis *

Neurological
- Polyradiculoneuritis



Chronic HBV infection

Reduced quality of life*

Ophthalmological
- Uveitis

Hematological
- Non-Hodgkin's lymphoma

Skin
- Oral lichen planus
- Pitted keratolysis
- Rheumatoid purpura

Renal
- Membranoproliferative glomerulonephritis *
- IgA nephropathy

Autoantibodies
- Anti-smooth muscle, anti-nuclear, anti-SSA/SSB

* Efficacy of HBV nucleos/tide analogues

Cacoub, P. & Asselah, T. (2022). Hepatitis B Virus Infection and Extra-Hepatic Manifestations: A Systemic Disease. *The American Journal of Gastroenterology, 117* (2), 253-263

Assessment of Chronic hep B patients

- History:
  - Particularly family history cirrhosis and/or HCC
  - Comorbidities: Metabolic risk factors, alcohol history, immunosuppression, possible extra hepatic manifestations
- Assessment of close contacts (partner and children)
- Examination: features of chronic liver disease/ comorbidities
- Special investigations and assessment of fibrosis:
  - Basic FBC, U&E, LFT, INR, alpha-fetoprotein – calculate APRI and FIB 4 scores
  - Hepatitis B serology including HepB VL, HBeAg and Anti-HBe
  - HIV
  - Hepatitis C and D (Assess Hep A immunity)
  - Transient elastography where available
- Liver imaging: USS with PV doppler
- Possible liver biopsy (reserved largely for research now) – may be considered with cofactors

APRI

- > 0.5 or TE > 7kPa equates to F2 fibrosis or higher
- >1 or TE > 12.5kPa equates to cirrhosis

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

Particular risks for HCC

Host Factors

- Older age and male
- Family history of HCC
- MASLD and particularly diabetes mellitus
- Longer duration of infection

Viral Factors

- Genotype – particularly $A_{1,}$ C and E
- High HBV DNA concentrations
- HBeAg +
- High HBsAg levels
- Basal pre-core and core – promotor mutations

Liver Factors

- Persistently raised ALT
- Cirrhosis
- HIV, HCV and HDV
- Concomitant liver disease of any cause

Environmental Factors

- Aflatoxin exposure
- Smoking and alcohol use

Patients for monitoring without therapy

ONLY IF:

1. **Normal ALT and no evidence of liver disease**
2. **No family history of cirrhosis or HCC**

Monitor using ALT, HBV DNA and non-invasive assessment of fibrosis

F/u intervals:

- HBeAg +ve & < 30 years age → F/u 3-6 monthly
- HBeAg -ve & DNA < 2 000 → F/u 6-12 monthly
- HBeAg -ve & DNA level ≥ 2000 → F/u 3 monthly x 1 year then 6 monthl

Treatment

Goals of treatment

- Acute Infection
  - Prevention of subacute or fulminant liver failure

- Chronic Infection
  - **Induction of long-term HBV DNA suppression and normalisation of ALT**
  - **Prevent or reverse disease progression to cirrhosis, end stage liver disease and/or HCC**

  - Prevent onward transmission particularly prevention of mother to child transmission
  - Prevent reactivation in at risk individuals
  - Treat and prevent extra hepatic manifestations of hepatitis B
  - Ultimately would like both eAg and sAg loss

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EASL CPG HBV. J Hepatol 2017;67:370–98

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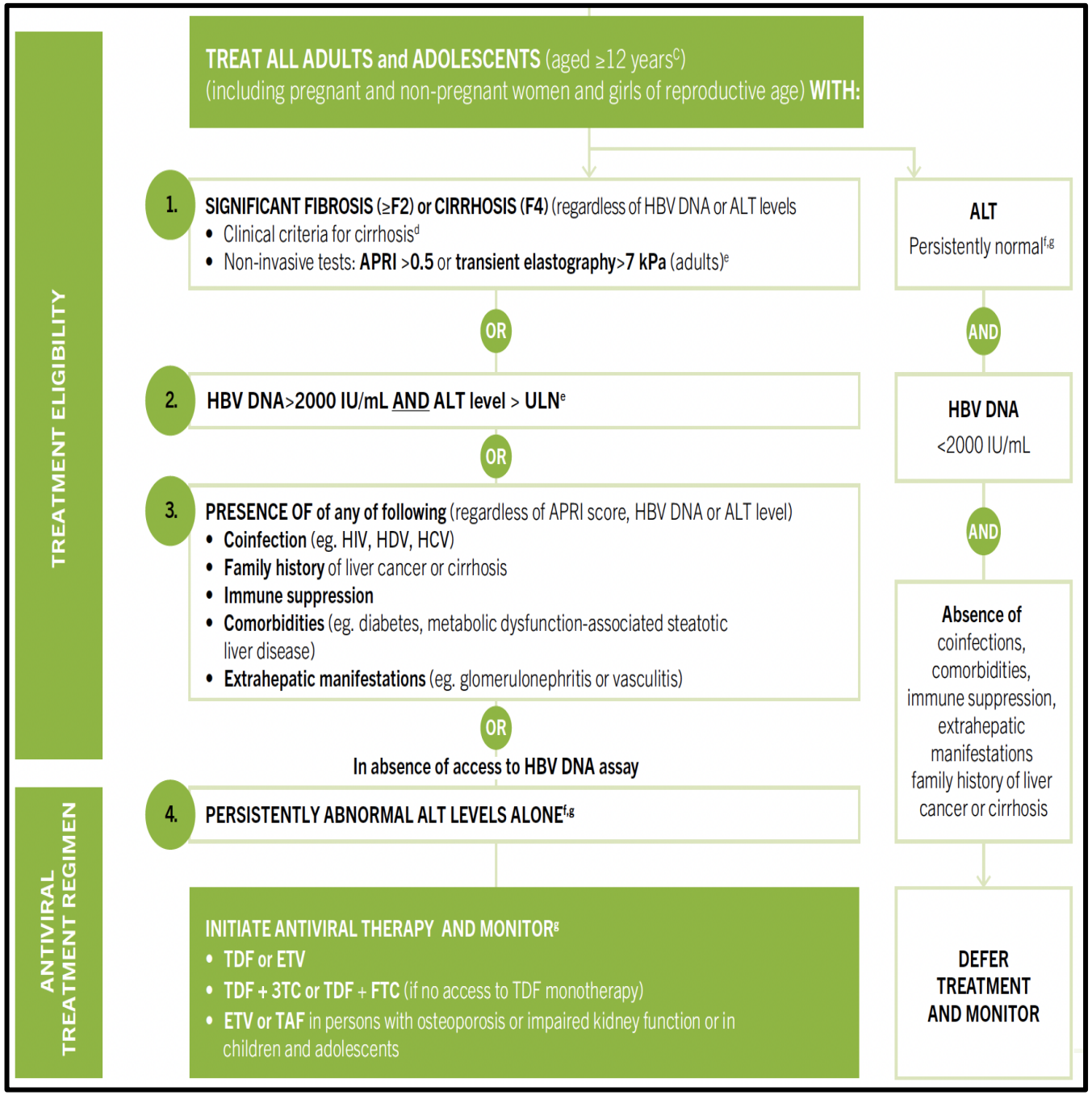
Who to treat – WHO 2024

1. Everyone with significant fibrosis or cirrhosis: Regardless of HBV DNA or ALT
   - APRI > 0.5 or TE > 7kPa - F2 or higher
   - APRI > 1 or TE > 12.5 kPa – F4/cirrhosis
2. HBV DNA > 2 000 IU/mL AND ALT > normal (male >30U/L; female > 19 U/L)
3. Presence of: Regardless of APRI score, HBV DNA , ALT
   - Coinfection with HIV, HCV, HDV
   - Family history of cirrhosis or HCC
   - Immune suppression
   - Comorbidities eg. DM and/or MASLD
   - Extra hepatic manifestations HBV
4. HBsAg positive and elevated ALT on 2 occasions over 6-12 month period – if no access to HBV DNA levels

World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection [Internet]. Geneva: World Health Organization; 2024 [cited 2025 Feb 1]. Available from: https://www.who.int/publications/i/item/9789240090903



WHO 2024 HBV Guidelines

Decentralise Diagnosis and Rx

Diagnostics

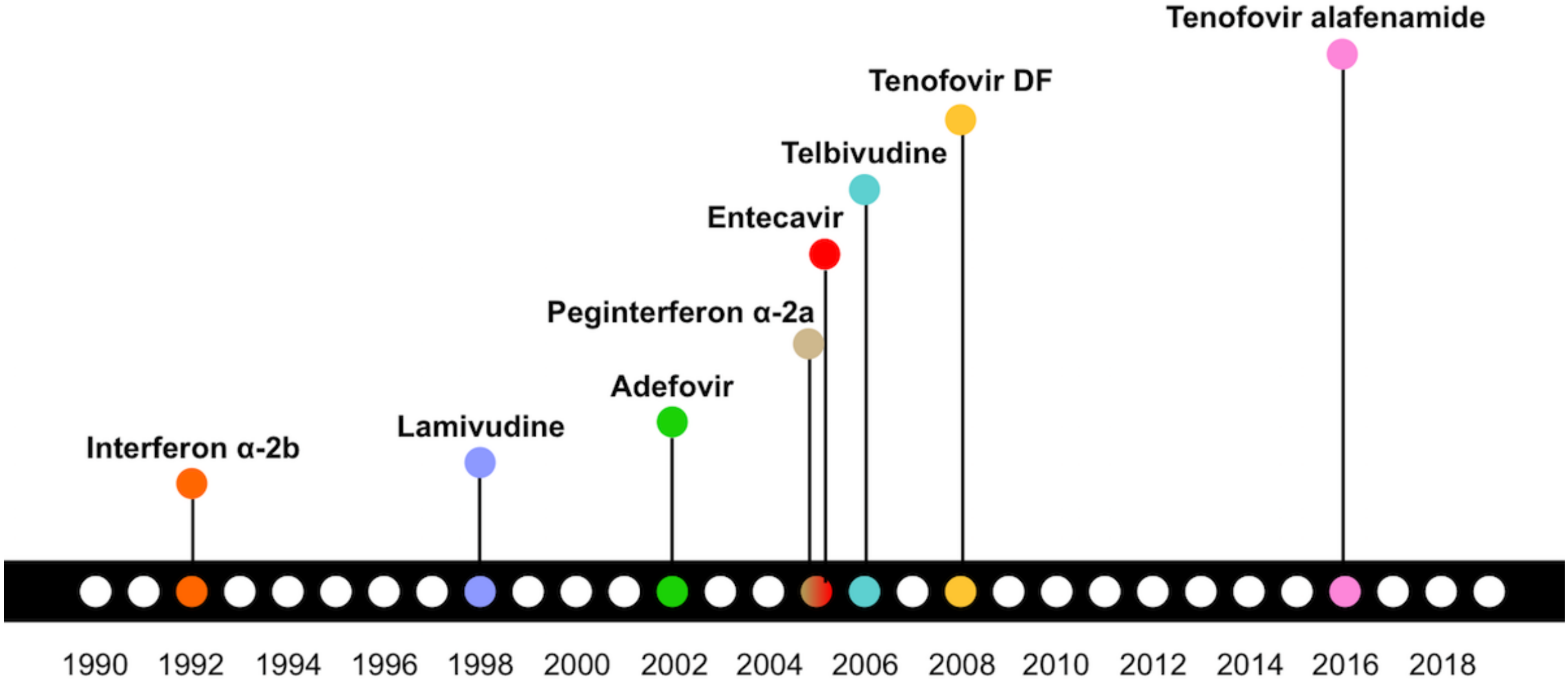
- POC HBsAg testing & Reflex HBV DNA
- Reflex anti-HDV and HDV RNA testing
- Clinic or Lab-based reflex testing

Diagnostic integration across programs using multi-disease testing platforms

- Existing platforms for HIV or HCV viral load or TB testing

World Health Organization

Hepatitis B treatment



Barriers to Resistance

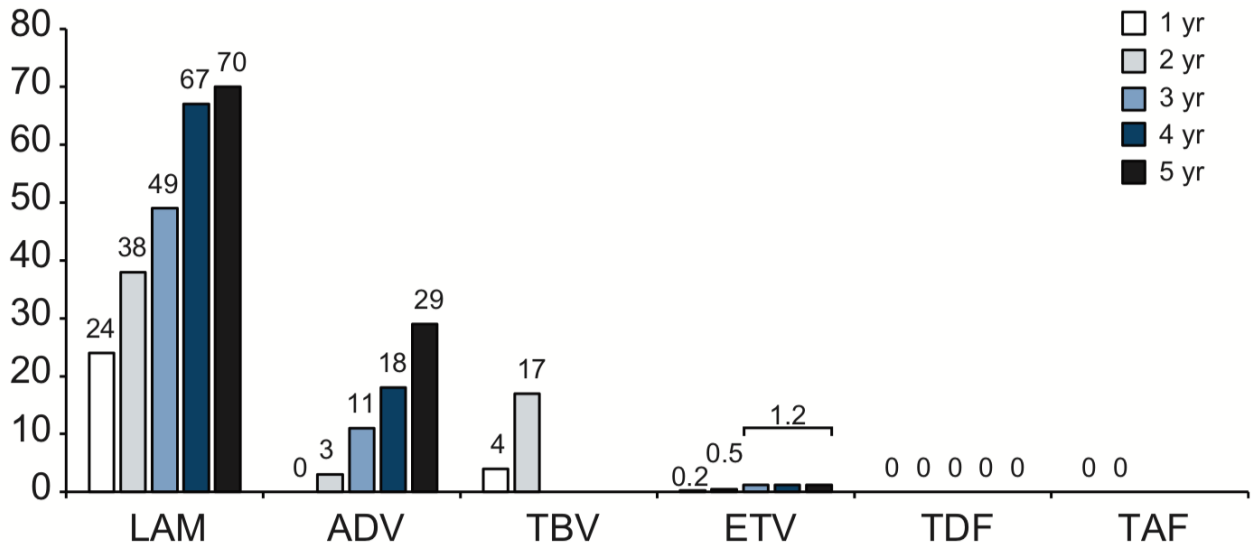


Fig. 3. Cumulative incidence of HBV resistance for lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (TBV), tenofovir (TDF) and tenofovir alafenamide (TAF) in pivotal trials in nucleos(t)ide-naïve patients with chronic hepatitis B. (Collation of currently available data – not from head-to-head studies). No evidence of resistance has been shown after 8 years of TDF treatment.[69]

European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-398.

Definitions of response to treatment

Responses	NA therapy	PegIFNα therapy
Virological (on-treatment)	**Response:** HBV DNA <10 IU/ml **Primary non-response:** <1 $\log_{10}$ decrease in HBV DNA after 3 months of therapy **Partial response:** HBV DNA decreased by >1 $\log_{10}$ but still detectable after ≥12 months of therapy in compliant patients **Breakthrough:** confirmed HBV DNA increase of >1 $\log_{10}$ above on-therapy nadir	**Response:** HBV DNA <2,000 IU/ml
Virological (off-treatment)	**Sustained response:** HBV DNA <2,000 IU/ml for ≥12 months after end of therapy	
Serological	HBeAg loss and development of anti-HBe* HBsAg loss and development of anti-HBs	
Biochemical	ALT normalization† (confirmed by ALT determination at least every 3 months for at least 1 year post-treatment)	
Histological	Decrease in necroinflammatory activity† without worsening in fibrosis compared with pre-treatment histological findings	

European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-398.

Functional Cure:

Undetectable HBsAg and unquantifiable serum HBV DNA for at least 24 weeks after completing a finite course of therapy

Therapeutic Outcome	Blood				Liver	
	HBV DNA	HBsAg	Anti-HBs *	Anti-HBc	cccDNA	Integrated DNA
Partial cure	−	+	−	−/+	+	+
Functional cure	−	−	−/+	−/+	+	+
Complete cure	−	−	−/+	−/+	−	+
Sterilizing cure	−	−	−/+	−/+	−	−

* Anti-HBs and anti-HBc are not required for defining therapeutic endpoints. Anti-HBs: antibody to HBV surface antigen; cccDNA: covalently closed circular DNA; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

Mak LY, Seto WK, Yuen MF. Novel Antivirals in Clinical Development for Chronic Hepatitis B Infection. Viruses. 2021 Jun 18;13(6):1169.

Nucleos(t)ide agents as therapy for HBV

- Multiple excellent options including: Lamivudine, Tenofovir disoproxil, Tenofovir alafenamide and Entecavir
- Note: varying barriers to resistance and drug side effects

- With potent NAs eg. Entecavir or Tenofovir
  - May achieve HBeAg seroconversion and HBV VL suppression – to continue for 1 year post seroconversion and can consider stopping treatment
    - To continue monitoring as 20% relapse
  - Only 3-5% of patients clear HBsAg at 10 years of follow up

- Patients with cirrhosis and/or HBeAg negative chronic hepatitis B require lifelong therapy

WHO 2024 guidelines for NAs

- Long term use of potent NA with a high barrier to resistance is recommended regardless of the severity of the liver disease
- Tenofovir disoproxil fumarate (TDF) and Entecavir (ETV) are the recommended first line NAs
- Tenofovir alafenamide (TAF) is recommended for people with established osteoporosis and/or impaired renal function.

Tenofovir

- Potent antiviral activity
- Effective in suppressing wild-type as well as lamivudine-resistant HBV
- Tenofovir recommended as **first line treatment** in treatment-naïve patients, and in patients with lamivudine, telbivudine or entecavir resistance, preferably as additional treatment in these patients.
- Two formulations:
    - TDF: Tenofovir disoproxil fumarate
    - TAF: Tenofovir alafenamide

- Tenofovir disoproxil side effects largely renal and bone related – requires careful monitoring
- Consider TAF in older patients > 60 yrs, established osteoporosis or renal dysfunction and in adolescents > 12 years
- NO DOCUMENTED CLINICAL RESISTENCE

TDF	TAF
25% oral bioavailability	40% oral bioavailability
300mg (needs high dose to concentrate in hepatocytes, WBC)	25mg – 90% lower serum circulating levels, but non-inferior efficacy
Decreased bone mineral density	-
Renal toxicity	-
Distributed to a wide range of tissues	Selective to WBC and hepatocytes (essentially where HIV and HBV replicate)

Agarwal K et al 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018 Apr;68(4):672-681.

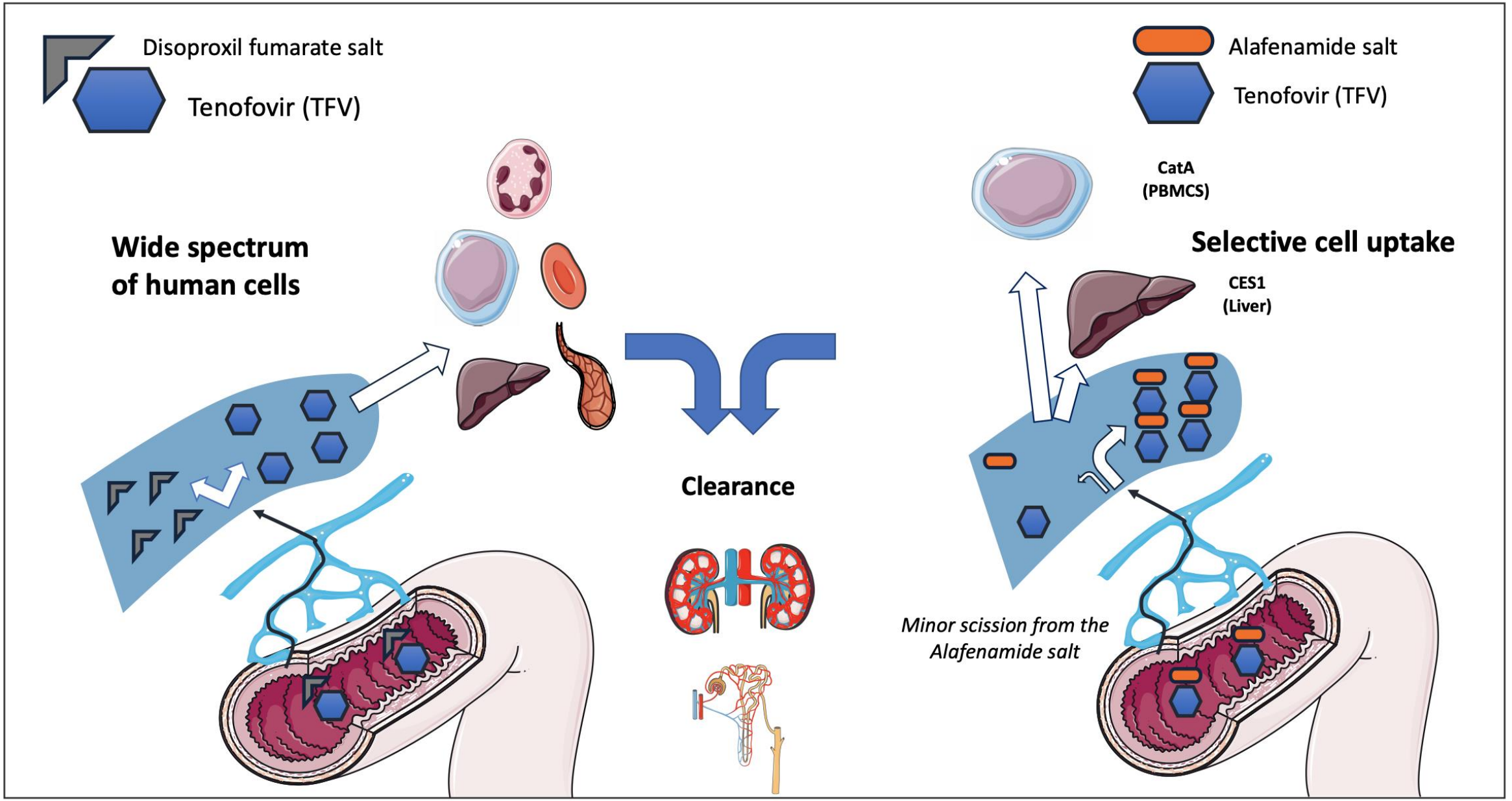
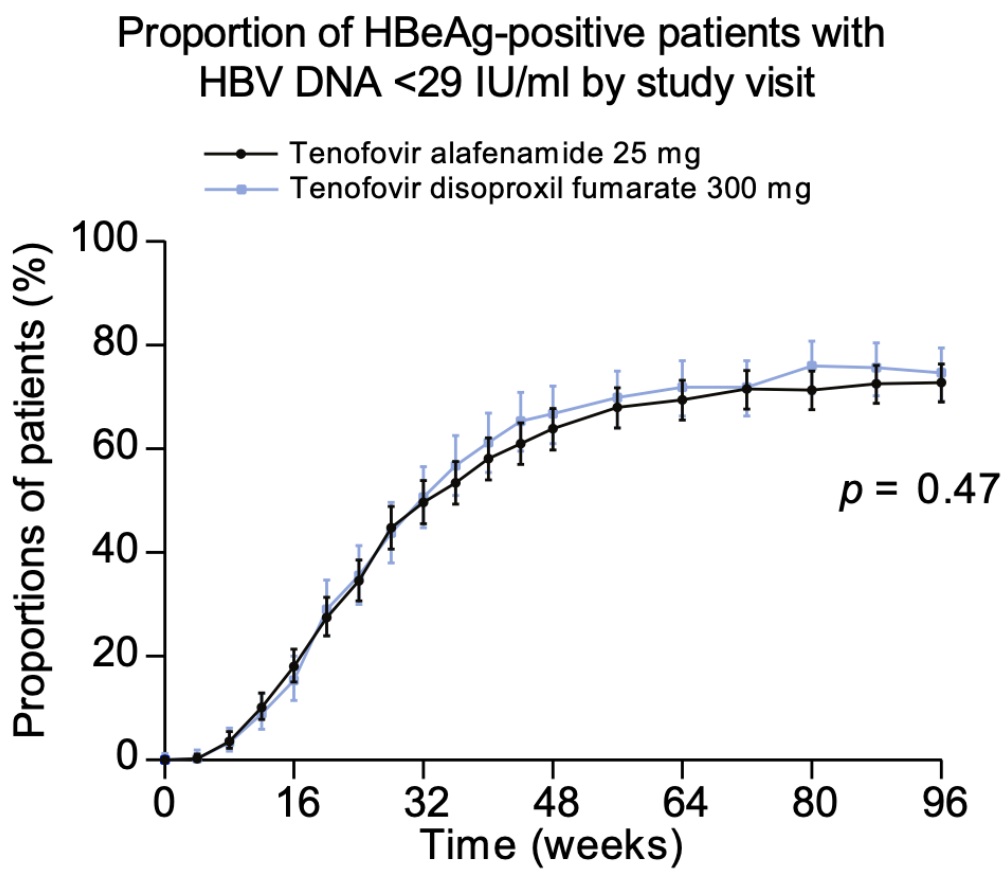


Figure 1 - The different tenofovir (TFV) distribution following intestinal absorption of Tenofovir disoproxil fumarate (TDF) and Tenofovir alafenamide (TAF) is represented.

Di Perri G. Tenofovir alafenamide (TAF) clinical pharmacology. Infez Med. 2021 Dec 10;29(4):526-529.

TDF vs TAF

A



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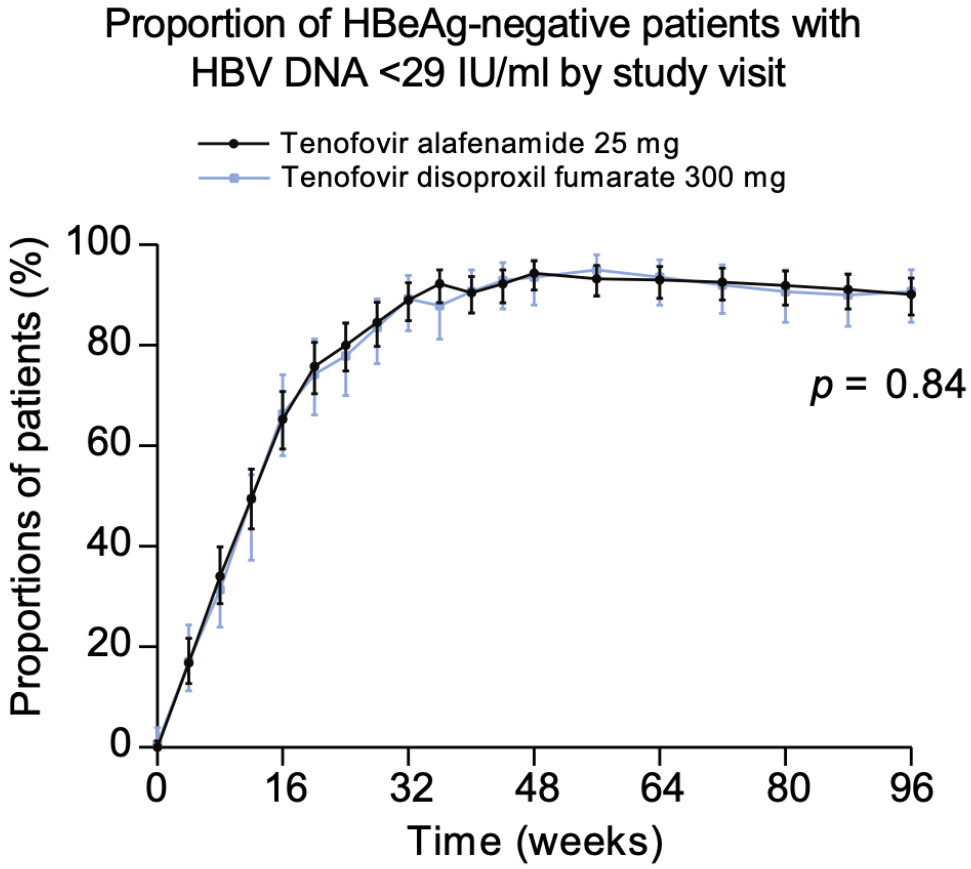


Agarwal K et al 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018 Apr;68(4):672-681.

Entecavir

- Nucleoside analogue approved by the FDA in 2005
- Potent inhibitor of HBV polymerase – only requiring dose of 0,5mg

- Differs from LAM in following ways at 52weeks of treatment in HBeAg positive patients
  - Superior virological response (viral suppression at 52 weeks ETV 67% vs LAM 36%)
  - Superior histological improvement (ETV 72% vs LAM 62%)
  - Superior ALT reduction (ETV 78% vs LAM 70%)
  - Similar HBeAg serocoversion rate (ETV 21% vs LAM 18%)

- In HBeAg negative patients:
  - Superior virological response (ETV 91% vs LAM 73%)
  - Superior histological improvement (ETV 70% vs LAM 61%)

- High genetic barrier to resistance (at 6 years only 1,2% resistance) – in those LAM naïve.
- **Much higher rates of resistance in those previously exposed to lamivudine**

Halegoua-De Marzio D, Hann HW. Then and now: the progress in hepatitis B treatment over the past 20 years. World J Gastroenterol. 2014 Jan 14;20(2):401-13.

Lamivudine

- First oral agent used in the treatment of HBV infection
- Nucleoside analogue that works as a DNA chain terminator
- Advantages
  - Lower cost compared to the other oral agents
  - Many years of experience confirming its safety, including its use during pregnancy and in renal failure
  - More rapid virus replication suppression, but entecavir and tenofovir are superior to lamivudine in suppressing viral replication long-term
- Disadvantage
  - High rate of drug resistance (look for YMDD mutation) - >50% have resistance at 5 yrs
  - Note dose 100mg recommended – In SA use 150mg
- Still significant role in patients co-infected with HIV (in whom lamivudine may be part of the antiretroviral regimen)

Emtricitibine

- Nucleoside analogue similar to lamivudine
- Approved for HIV in USA, but not for CHB.
- Intermediate genetic barrier to resistance – at 2 years 13% resistance.

Halegoua-De Marzio D, Hann HW. Then and now: the progress in hepatitis B treatment over the past 20 years. World J Gastroenterol. 2014 Jan 14;20(2):401-13.

Are combination therapies more efficacious?

TDF vs TDF/FTC

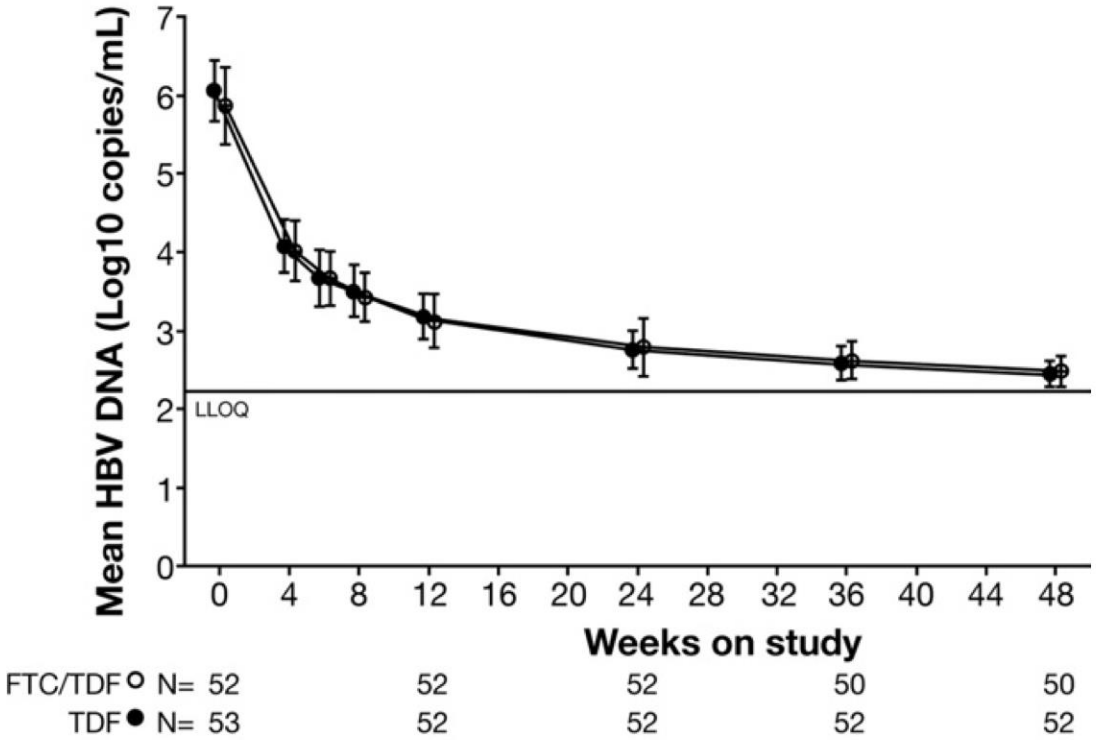


Figure 1. Mean (95% confidence interval) HBV DNA (log_{10} copies/mL) by study visit (RAT analysis set) and initial treatment assignment.

Berg T, Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic-hepatitis B virus infection. Gastroenterology. 2010 Oct;139(4):1207-17.

Treatment strategies for chronic hepatitis B

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss*
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment AEs[†]	Probably not[‡]
Contraindications	Many[§]	None[‖]
Strategy	Induction of a long-term immune control	Inhibition of viral replication
Level of viral suppression	Moderate	Universally high
Effect on HBeAg loss	Moderate[¶]	Low in first year, moderate over long term
Effect on HBsAg levels	Variable[¶]	Low**
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance	No	Minimal to none[††]

European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-398.

Problems with interferon's

- Severe side effects (up to 50% of patients)
  - Flu-like symptoms following each injection
    - fever, headache, muscle aches, pains (articulation, abdominal, back pain)
  - General fatigue
  - Gastrointestinal disorders
  - Thrombocytopenia and neutropenia
  - Thyroid dysfunction
  - Depressive episodes (can be very severe and lead to suicidal behavior)
- Contraindications
  - Fulminant or decompensated liver failure
  - Pregnancy
  - Extra hepatic manifestations, seizures, autoimmune disease

Monitoring on treatment with NAs

- **6 monthly:**
  - FBC, Creatinine, LFT, AFP
  - HBV VL
  - APRI score
  - USS for HCC screening if advanced fibrosis or cirrhosis
- **Annually:**
  - Transient elastography to assess degree of fibrosis and monitor for progression
  - HBsAg and HBeAg/HBeAb
  - USS
- **More frequent follow up for certain patients:**
  - Those with advanced disease particularly cirrhosis (compensated or decompensated)
  - HIV + patients
  - Renal impairment
  - Adherence concerns
  - Anyone with increased risks for HCC

Monitoring if treatment not indicated

<u>HBeAg negative infection and HBeAg positive infections</u>

4 monthly monitoring for first year

- ALT, AST
- Platelets

To confirm phase of infection not requiring NA treatment and thereafter

HBeAg negative infection: Annual

- FBC, Creatinine, LFT, AFP
- HBV VL
- APRI score
- USS

HBeAg positive infections: 6 monthly

- FBC, Creatinine, LFT, AFP
- HBV VL
- APRI score
- Annual USS

Screening for HCC

- Detect tumors <3cm for curative therapy
- Surveillance with **liver USS and serum AFP 6 monthly**
  - all cirrhotic patients and advanced fibrosis
  - individuals with family history of HCC
  - any patient with other HCC risk factors eg MASLD, Iron overload

HIV-HBV co-infection

- Significantly more **aggressive disease course**
  - Increasing viral replication and reactivation
  - Increased risk of acute liver failure
  - Increased risk of developing CHB or occult hepatitis B
  - Accelerated progression to fibrosis and cirrhosis
  - Increased rate of HCC and at a younger age

- **ART related issues**
  - Increased risk of ART hepatotoxicity
  - Hepatitis B viral flare possible with IRIS on HAART therefore must include treatment active against HBV as well (particularly with CD4 <350)
  - Remember to continue HBV treatment if/when changing HAART

- HIV-HBV mortality 2x greater than HIV-HCV mortality
- CD4 count <200 cells/mL 16 times greater liver-related deaths than CD4 count >350cells/mL
- Increased risk of perinatal HBV infection

Spearman CW, Sonderup MW, et al; Gastroenterology and Hepatology Association of sub-Saharan Africa (GHASSA). Hepatitis B in sub-Saharan Africa: strategies to achieve the 2030 elimination targets. Lancet Gastroenterol Hepatol. 2017 Dec;2(12):900-909.

HCV- and HDV-HBV coinfection

- **Hepatitis C**
  - Accelerates progression of liver disease and HCC
  - HCV usually greater contributor to liver disease
  - SVR rates with DAAs in mono-infected vs co-infected patients comparable
  - Treat Hepatitis B prior to initiating HCV treatment
    - All those that qualify for CHB treatment – initiate first
    - If CHB and do not qualify – Treat and consider stopping NAs 12 weeks post DAA therapy
    - Occult hepatitis B – Monitor closely and investigate for reactivation if rising ALT
- **Hepatitis D**
  - Defective virus – only able to infect those who are HBsAg +
  - Affects 5% of people with CHB globally

European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-398.
Jeng WJ, Papatheodoridis GV, Lok ASF. Hepatitis B. Lancet. 2023;401(10381):1039-52

PMTCT

- Risk of Vertical transmission is high if HBeAg positive or HBV DNA >200 000 IU/ml
- Co-infection with HIV increases risk 2.5 times
  - More likely to be HepBeAg + and have higher HBV VL
- Annually 1% of newborns are infected with HBV in SSA

- Recent adoption of policy for HBsAg screening in pregnancy in SA
- WHO recommends screening if prevalence >2%
- HBV screening should be done in 1st trimester
- Those not vaccinated should be vaccinated
- Ideally all babies should receive birth dose vaccine within 24 hours of delivery – followed by 2 – 3 further doses
- Breastfeeding is not contraindicated

Spearman CW et al, Gastroenterology and Hepatology Association of sub-Saharan Africa (GHASSA). Hepatitis B in sub-Saharan Africa: strategies to achieve the 2030 elimination targets. Lancet Gastroenterol Hepatol. 2017 Dec;2(12):900-909.

Recommendations: Preventing HBV Mother-to-child Transmission

Updated recommendation

In settings where HBV DNA or HBeAg testing is available, *Prophylaxis with TDF is recommended for HBV-positive (HBsAg-positive) pregnant women with **HBV DNA ≥200 000 IU/mL or positive HBeAg**

(strong recommendation, moderate-certainty evidence)

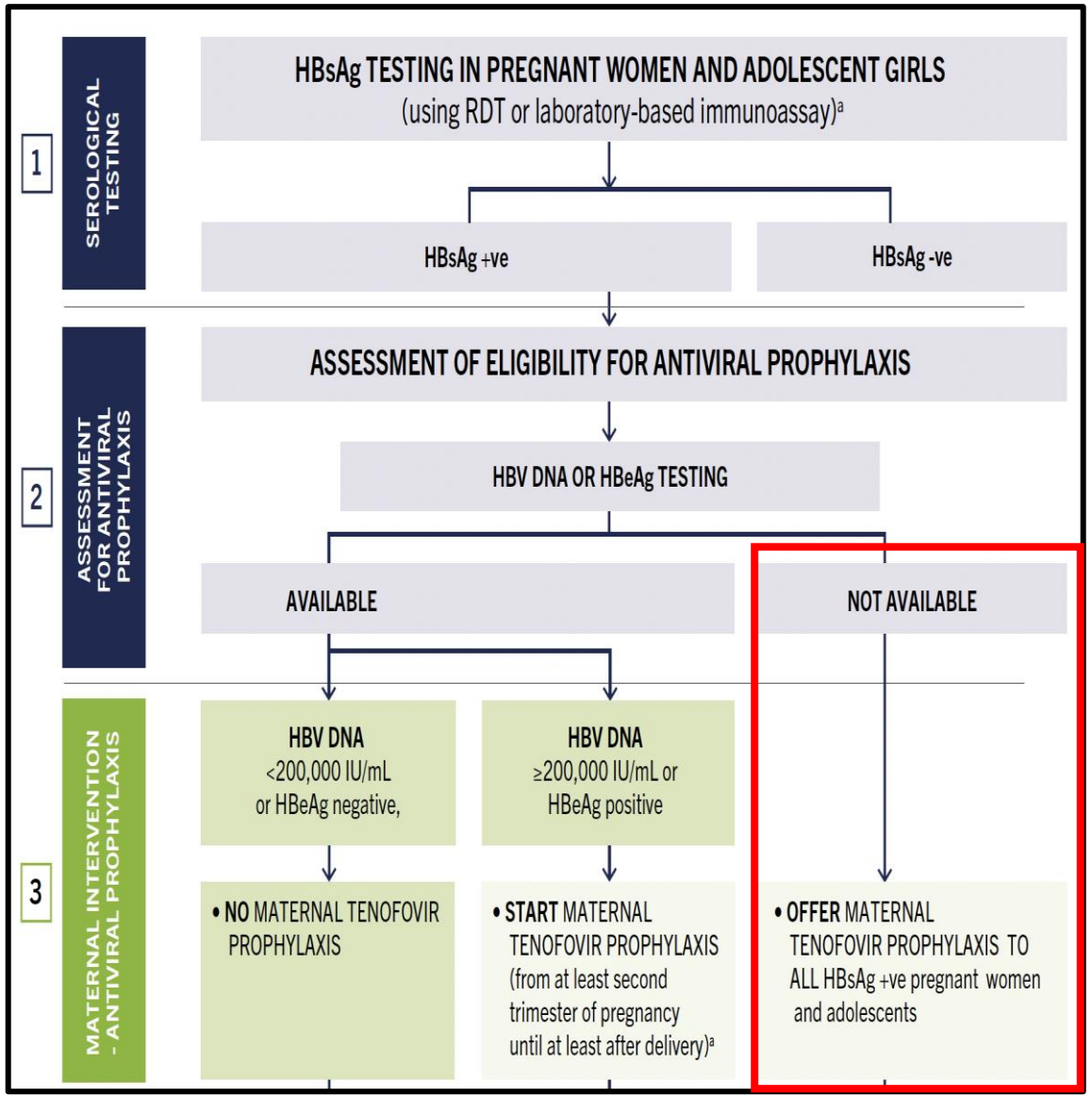
New 2024 recommendation

In settings where neither HBV DNA nor HBeAg testing is available, *Prophylaxis with TDF for **all HBV-positive (HBsAg-positive) pregnant** women may be considered

(conditional recommendation, low-certainty evidence)

*Preferably **from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series)**, to prevent MTCT of HBV. Can be continued if planning future pregnancies.

All interventions should be given in addition to at least three doses of hepatitis B vaccination for all infants, including a timely birth dose.



Vaccination

- Most cost-effective way to prevent hepatitis B infection
- Safe, very effective, can be given in combination with other vaccinations
- HBsAb are long lasting (>30 years) – boosters not recommended
- Age and immune competency most important factors influencing immunologic response to vaccination
- >95% will reach protective levels (>10 mIU/mL) after 3 doses
- If over 60 years only 60 – 75% will develop immunity
- Factors effecting vaccine efficacy: obesity, smoking, genetic, CKD, DM
- Non-response:
  - Repeat course with same vaccine – can double the dose
  - Can use plasma derived vaccine – higher response rates
  - Note: consider double dose vaccination in HIV + with low CD4 and immunosuppressed patients

Jeng WJ, Papatheodoridis GV, Lok ASF. Hepatitis B. Lancet. 2023;401(10381):1039-52.

Looking to the future

Functional Cure:

Undetectable HBsAg and unquantifiable serum HBV DNA for at least 24 weeks after completing a finite course of therapy

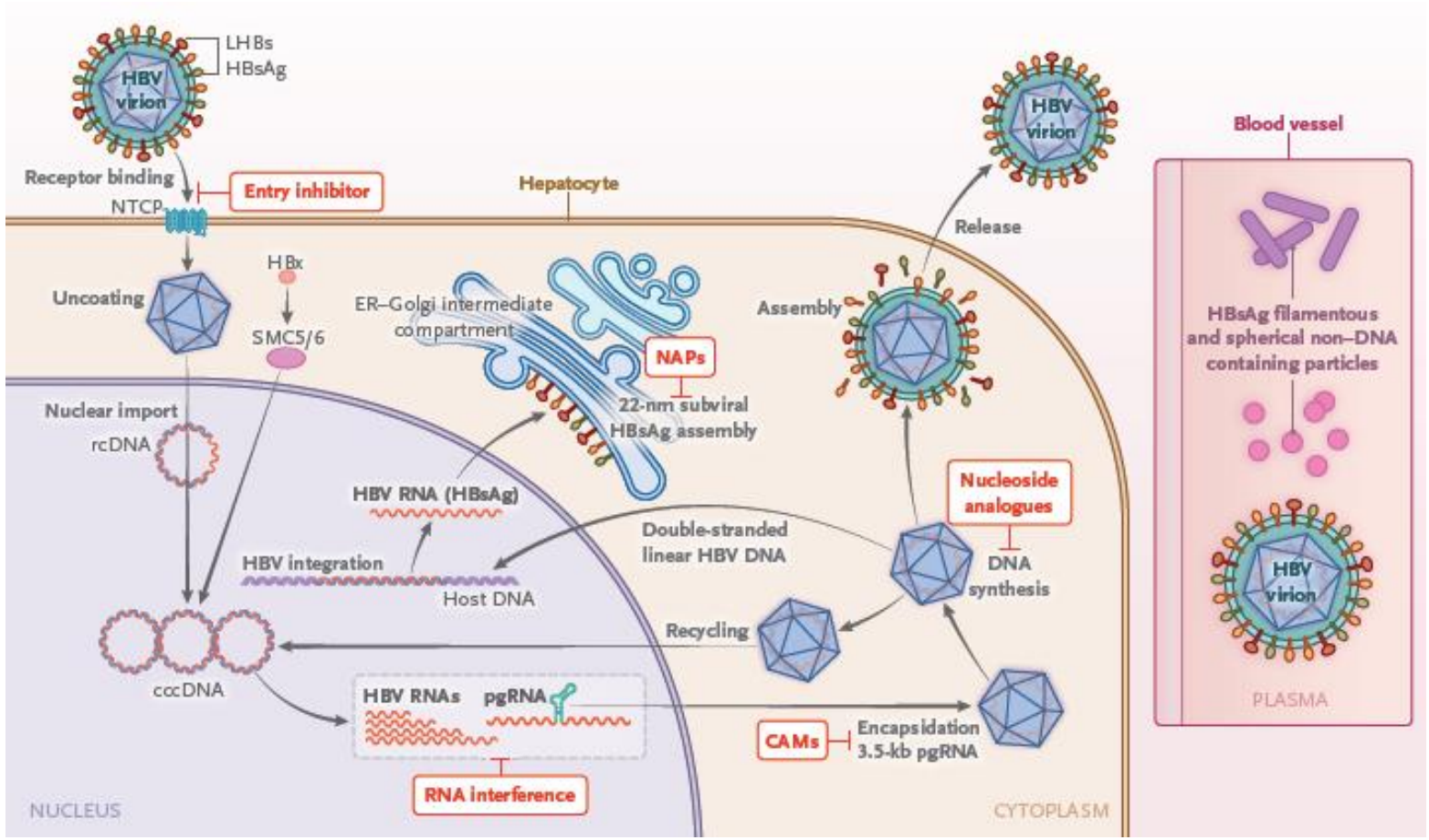
Therapeutic Outcome	Blood				Liver	
	HBV DNA	HBsAg	Anti-HBs *	Anti-HBc	cccDNA	Integrated DNA
Partial cure	−	+	−	−/+	+	+
Functional cure	−	−	−/+	−/+	+	+
Complete cure	−	−	−/+	−/+	−	+
Sterilizing cure	−	−	−/+	−/+	−	−

* Anti-HBs and anti-HBc are not required for defining therapeutic endpoints. Anti-HBs: antibody to HBV surface antigen; cccDNA: covalently closed circular DNA; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

Mak LY, Seto WK, Yuen MF. Novel Antivirals in Clinical Development for Chronic Hepatitis B Infection. Viruses. 2021 Jun 18;13(6):1169.

Will likely need triple therapy:

1. Halt viral replication
2. Address cccDNA
3. Boost the immune system



Dusheiko G, Agarwal K, Maini MK. New Approaches to Chronic Hepatitis B. N Engl J Med. 2023;388(1):55-69.