GILEAD
Creating Possible

Hepatitis B: Breaking the silence around a hidden epidemic

ZA-UNB-0177 V1 Approved February 2026

Disclaimer

- This meeting is intended for healthcare professionals only and may not be attended by anyone who is not a healthcare professional.
- This presentation is prepared and delivered by Dr. Michael Reid, Medical Director at Gilead Sciences South Africa and Dr. Ntsakisi Maluleke, Medical Manager at Gilead Sciences South Africa..
- The content presented is for educational purpose. Most of the slides will discuss HCV disease and elimination. Some slides will touch on Gilead product, as this is the available treatment in South Africa.
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- Patient management decisions are the responsibility of the individual provider in accordance with each case's specific circumstances.

Introduction

Hepatitis B Introduction

Hepatitis

Inflammation of the liver, caused by a virus or a toxin

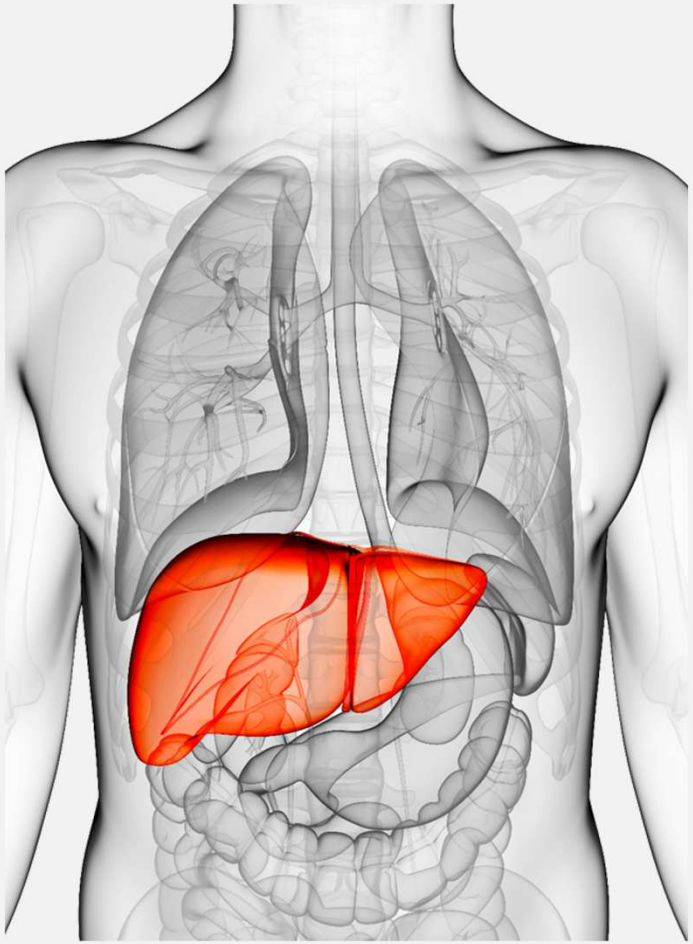
Acute hepatitis B

Short-term infection with hepatitis B virus which the body's immune system clears within 6 months

Chronic hepatitis B

Long-term infection where the body is unable to clear the virus itself. Generally defined as the presence of HBsAg for > 6 months

HBsAg = surface antigen of the hepatitis B virus

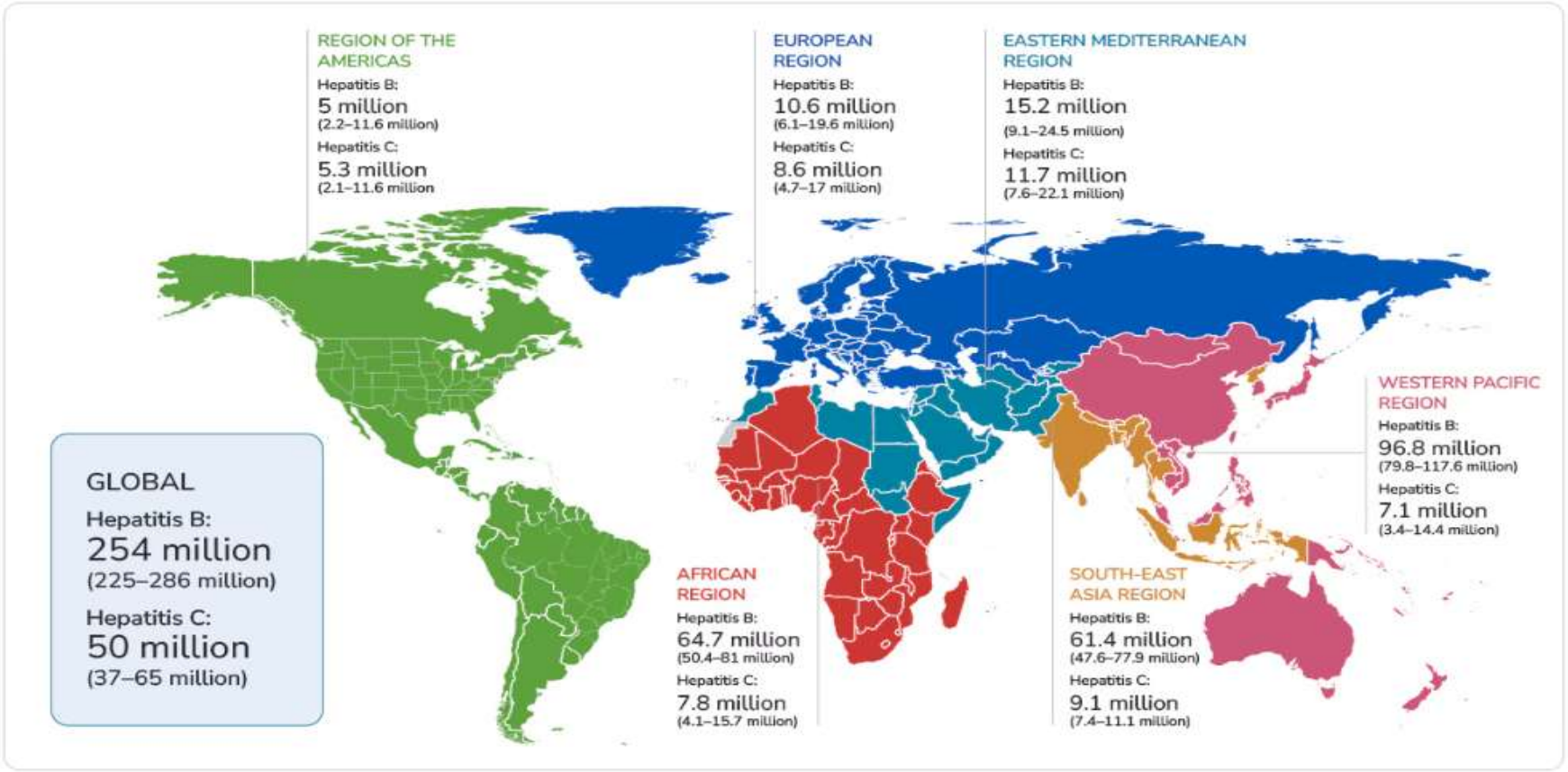


Lok A, *Hepatology* 2001

Epidemiology of HBV

Geographical Distribution

Estimates of the burden of chronic hepatitis B and hepatitis C by WHO region, 2022



https://www.cdc.gov/hepatitis/global/index.html

South African HBV infections at a glance (2024)

Prevalence:
n=3 692 025, (6%)

Diagnosed
42%

Annual Treated
23%

Annual Deaths
26 084

Deaths per hour
3

Birth Dose
<1%

3+ Doses
74%

HBIG
<1%

Pregnant Tx
11%

Polaris Observatory: https://cdafound.org/polaris/dashboard/

WHO Global Health Sector Strategy: 2030 Targets for HBV

Prevention targets

- 90% of infants have HBV birth dose vaccination
- 100% of blood donations screened
- 90% have access to safe injections

***SA progress- Prevention targets**

- 0% of infants have HBV birth dose vaccination
- 100% of blood donations screened
- 95% have access to safe injections

Testing targets

- 90% of people aware of infection

***SA progress- Testing targets**

- 42% of people aware of infection

Treatment targets

- 80% of eligible persons with CHB treated

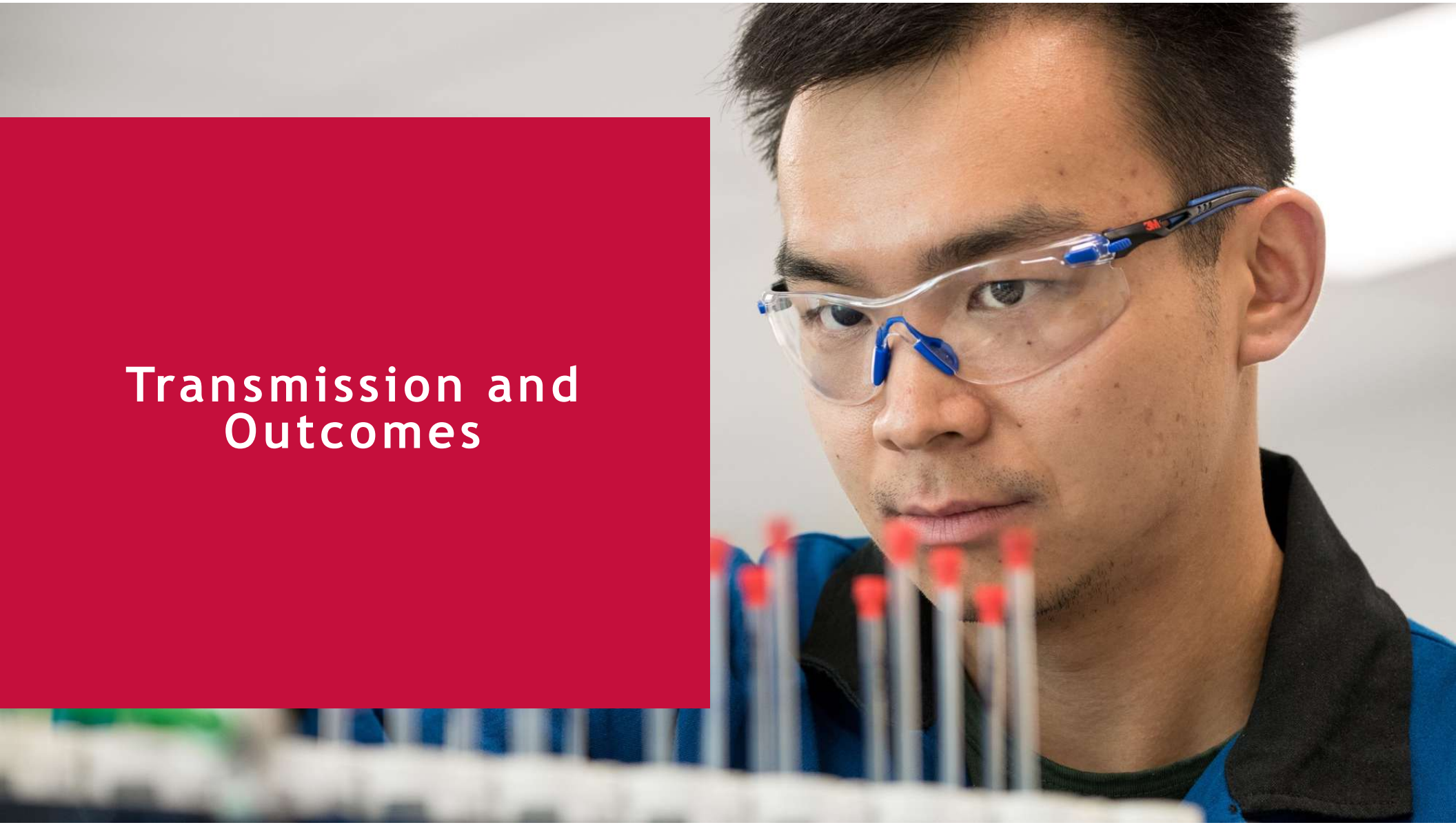
***SA progress- Treatment targets**

- 23% of eligible persons with CHB treated

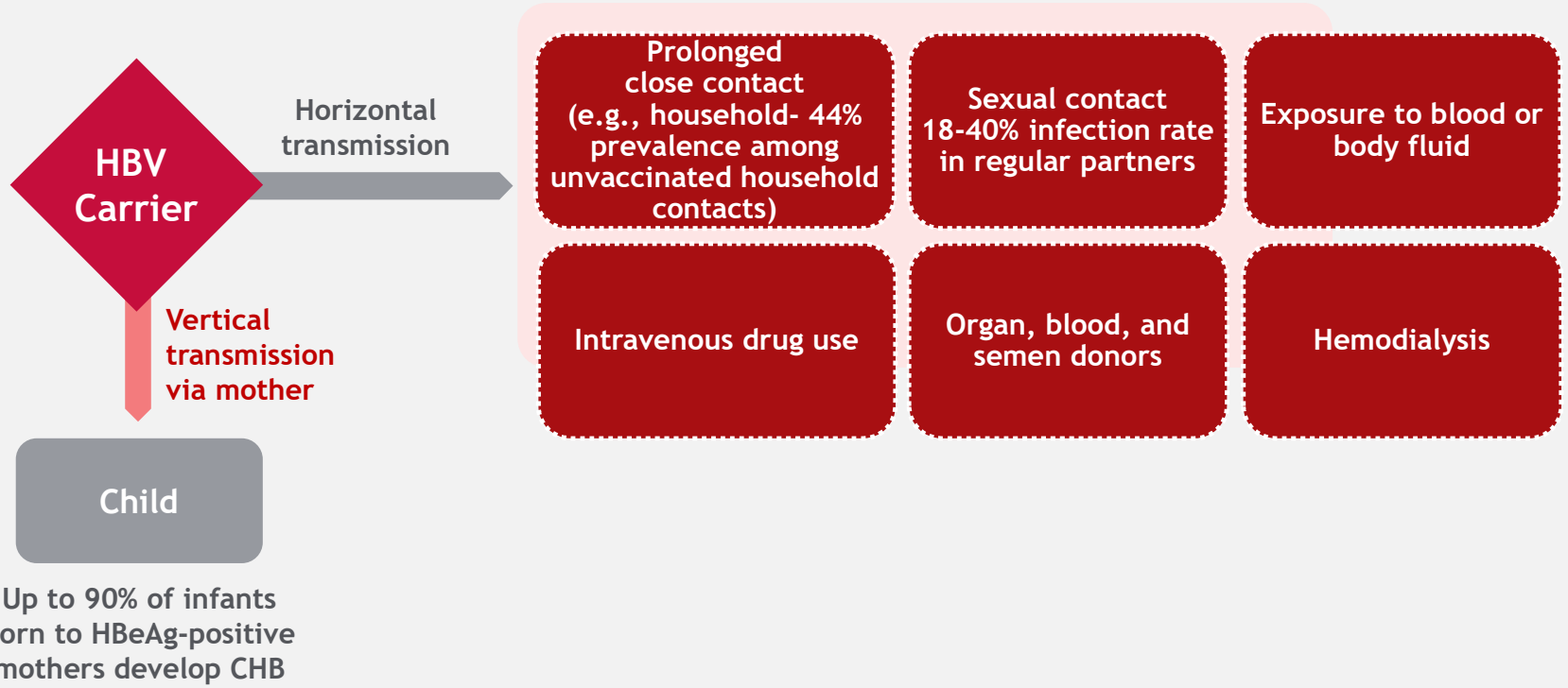
*Polaris Observatory: https://cdafound.org/polaris/dashboard/

WHO. Global health sector strategy on viral hepatitis 2016–2021
Available at: http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1

Transmission and Outcomes

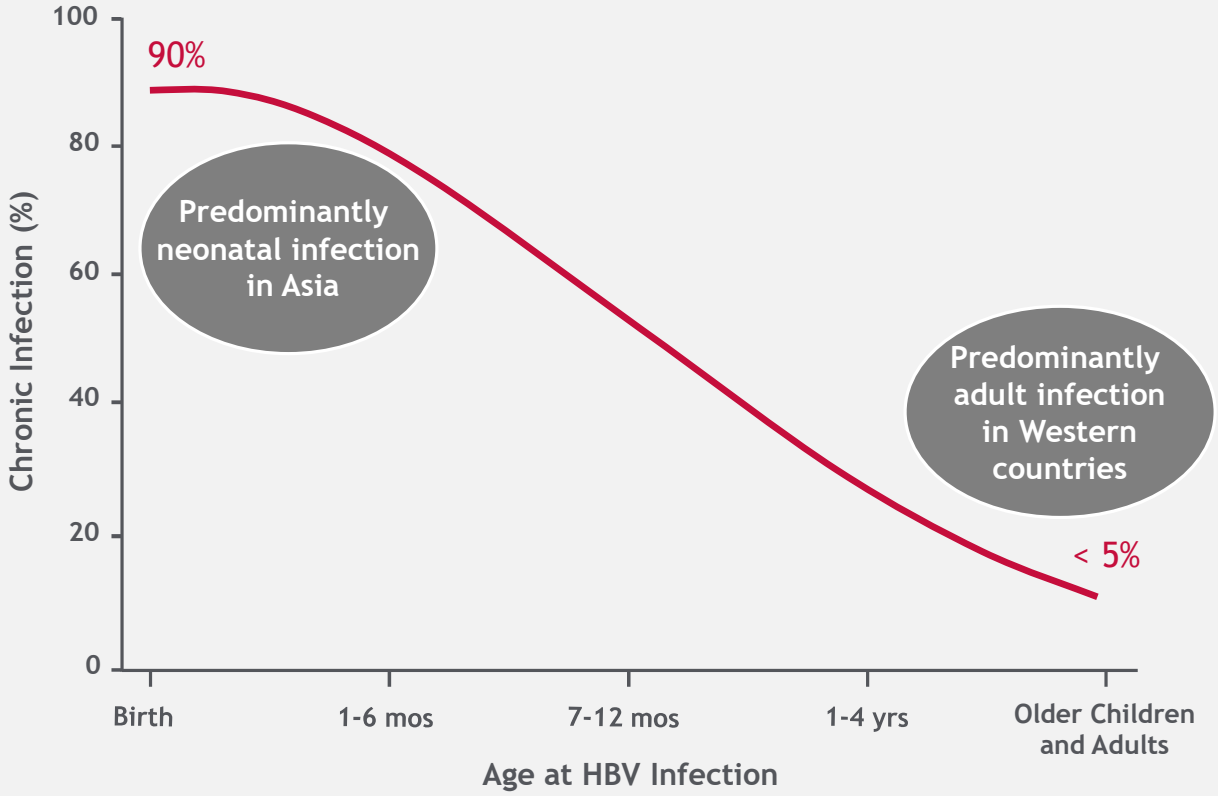


Modes of HBV Transmission and Persons at Risk

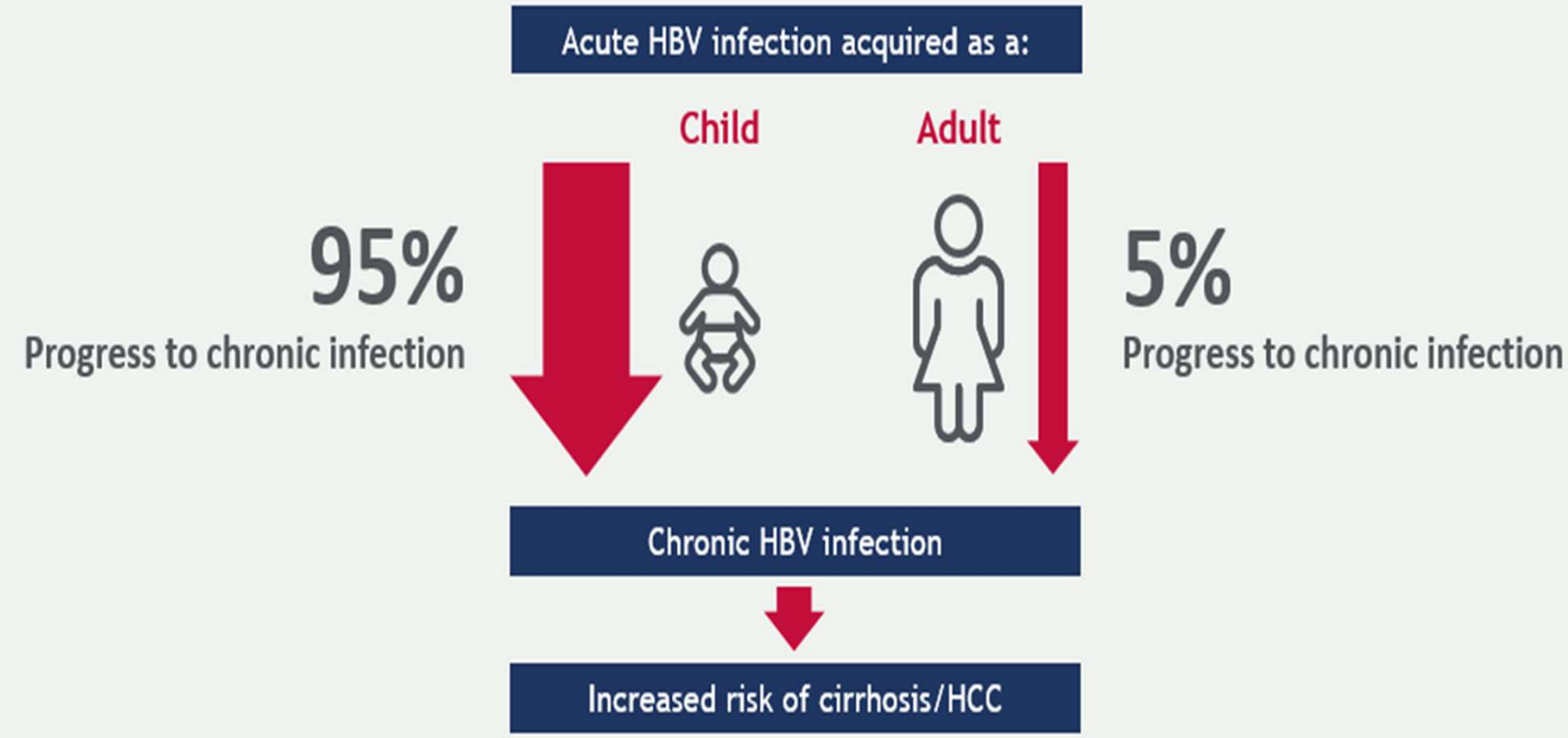


WHO 2015. CDC 2015. Mast 2006. Buchanan 2010. Weinbaum 2008.

Progression to Chronic Infection is Dependent on the Age at Acute HBV Infection

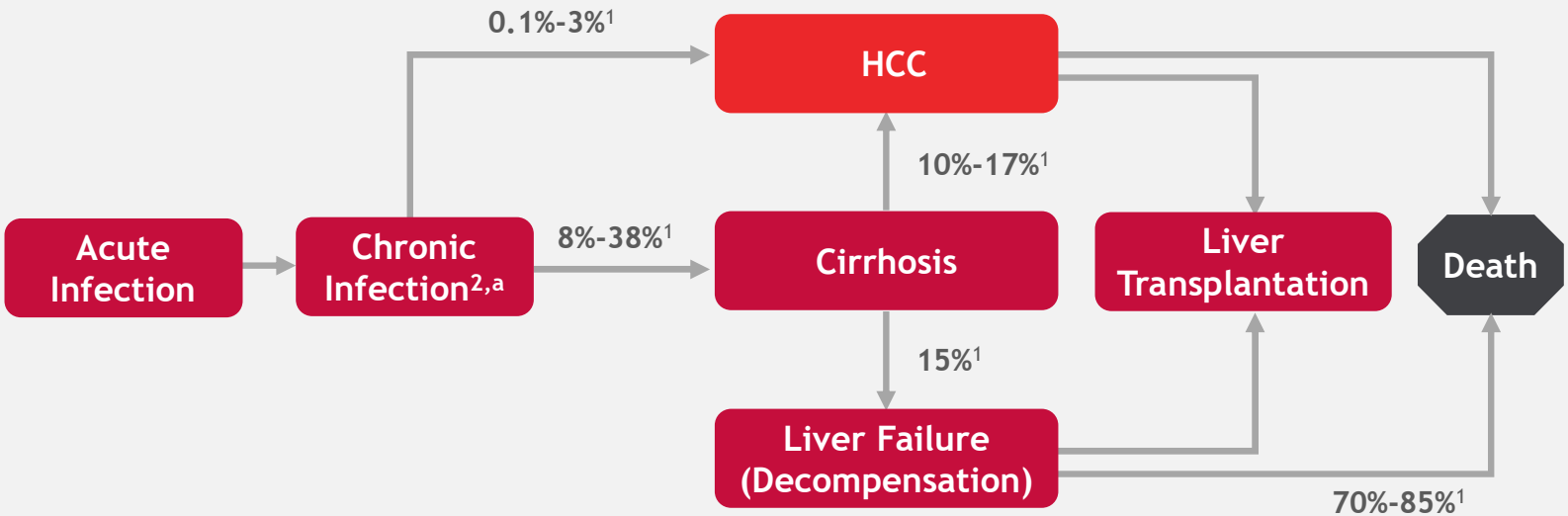


Asian Liver Center. *2007 Physician's Guide to Hepatitis B: A Silent Killer*. http://liver.stanford.edu/files/2007Handbook.pdf. Accessed November 7, 2007.



CHB Is Associated With Severe Burden of Disease

Five Year Cumulative Incident Rates of Development of CHB Complications



CHB, chronic hepatitis B; HCC, hepatocellular carcinoma

[a]Patient is chronically infected if HBsAg+ for ≥ 6 months.

1. Fattovich G, et al. *J Hepatol*. 2008;48:335-352.
2. Lok ASF, McMahon BJ. *Hepatology*. 2009;50:1-36.

Figure adapted with permission from Fattovich G, et al. In: Marcellin P, ed. *Management of Patients With Viral Hepatitis*. Paris: APMAHB; 2004.

Outcomes

Adult infection:

20-30% of adults who are chronically infected will develop **cirrhosis and/or liver cancer**

< 5% of adults with acute hepatitis B will go on to develop **Chronic Hepatitis B (CHB)**

In infants and children infection:

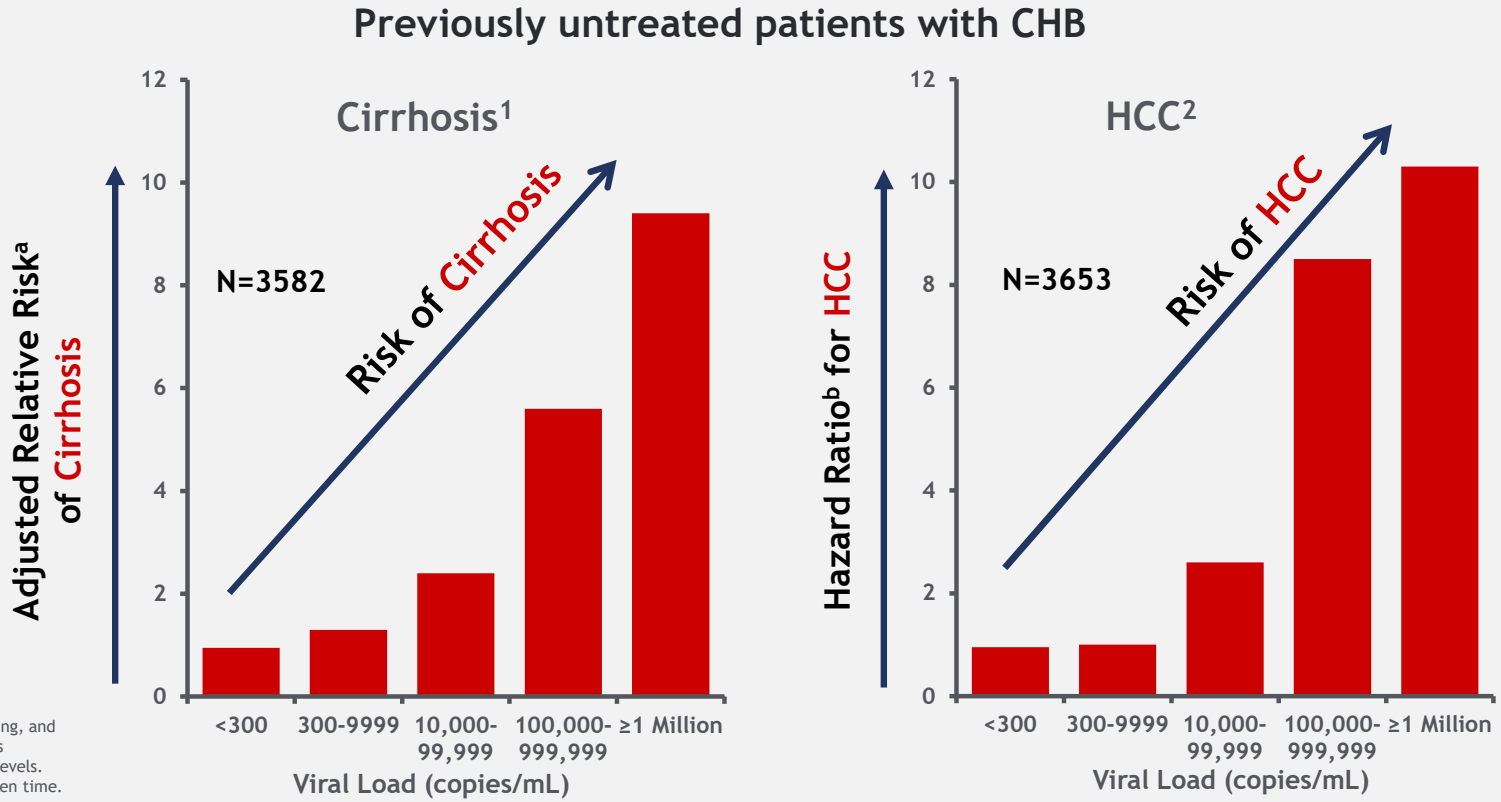
80-90% of infants infected **during the first year of life** develop **chronic infections**

30-50% of children infected **before the age of 6 years** develop **chronic infections**

World Health Organization. Hepatitis B. Fact Sheet http://www.who.int/news-room/fact-sheets/detail/hepatitis-b Accessed November 2020.

Higher HBV DNA Levels Are Associated With Increased Risk of Cirrhosis and HCC (REVEAL Study)

- Prospective cohort study of 3653 participants (aged 30-65 years), who were seropositive for the hepatitis B surface antigen
- Recruited to a community-based cancer screening program in Taiwan between 1991 and 1992.



CHB, chronic hepatitis B;
HCC, hepatocellular carcinoma

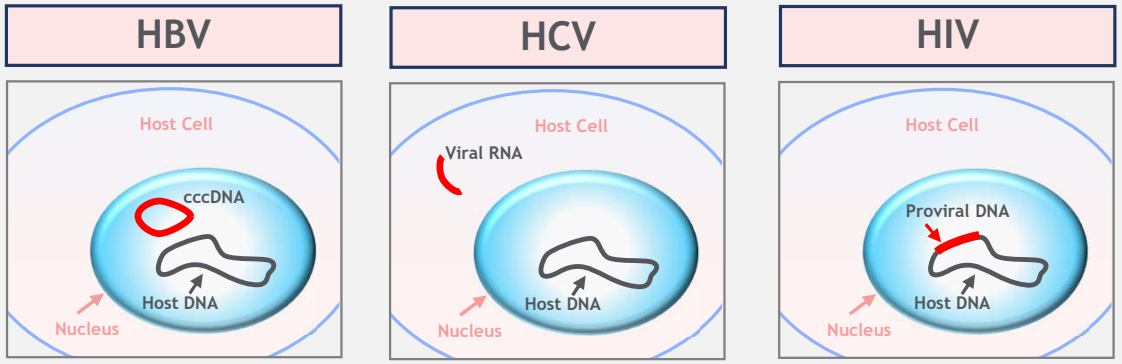
[a]Adjusted for age, sex, cigarette smoking, and alcohol consumption; risk of cirrhosis is independent of HBeAg status and ALT levels.
[b]Relative risk of an endpoint at any given time.

1. Iloeje UH et al. *Gastroenterology*. 2006;130:678-686.
2. Chen CJ et al. *JAMA*. 2006;295:65-73.

Elevated serum HBV DNA level (≥10 000 copies/mL) is a strong risk predictor of hepatocellular carcinoma independent of HBeAg, serum alanine aminotransferase level, and liver cirrhosis.

HBV Virology and Serology

Viral Characteristics



Treatment Goal: Life-long viral suppression

Treatment Goal: SVR

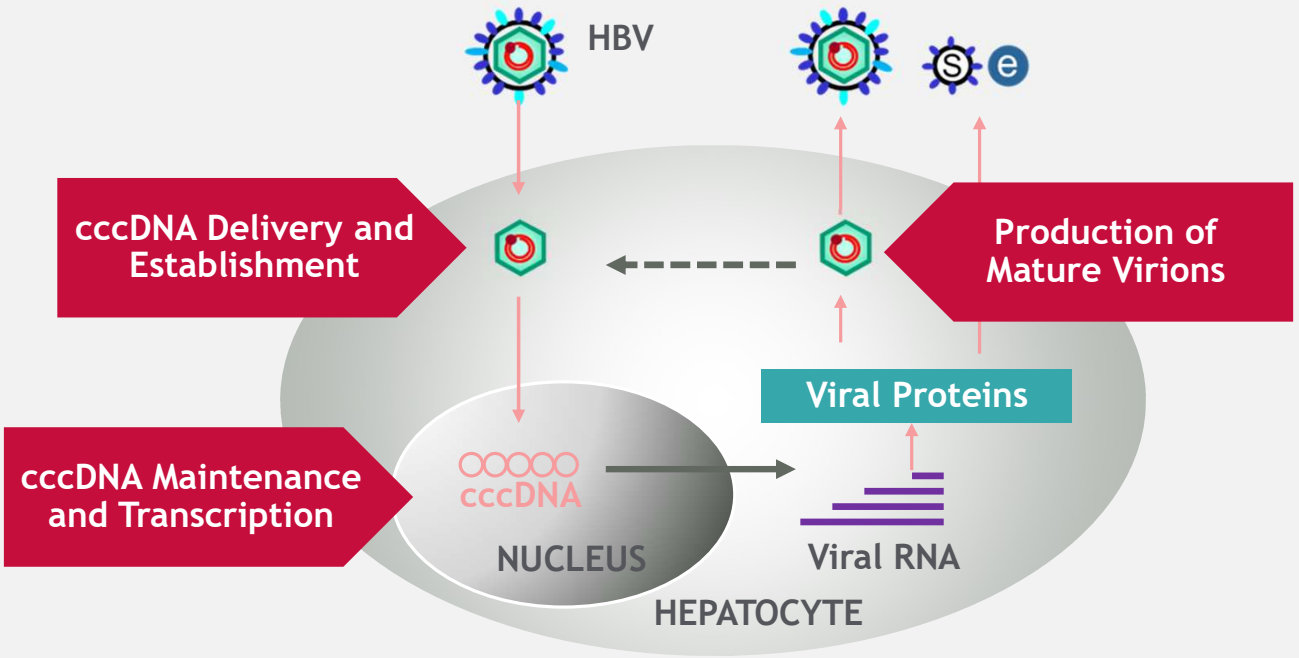
Treatment Goal: Life-long viral suppression

	HBV	HCV	HIV
Virus type	**DNA *Hepadenovirus***	**RNA *Flavivirus***	**RNA Retrovirus**
Mutation rates	10^{-5}	10^{-3}	10^{-4}
Eradication possible with therapy?	Not yet	Yes-Sustained virologic response (cure)	No- Latent reservoirs
Viral targets	Hepatocytes	Hepatocytes	Mainly CD4+ cells
Variants	8 genotypes A-H	6 genotypes 1-6	HIV 1 and 2, 3 groups, clades
Pathogenesis	Host immune altered or insufficient response	Host immune response	Damage to host immune system

SVR, sustained virologic response

Liaw Y-F and Chu C-M. *Lancet* 2009; 373: 582-592; Dandri M and Locarnini S. *Gut* 2012; 61(Suppl 1): i6-i17; Locarnini S. 2004; 24(Suppl 1): 3-10; Chinen J and Shearer WT. *J Allergy Clin Immunol* 2002; 110(2):189-198; Chisari F V. *Nature* 2005; 436: 930-932

HBV Replication Cycle



1. HBV virus and the host cell fuse together at the cell surface
2. The capsid of the virus goes through endocytosis.
3. Viral genome transported to the nucleus.
4. cccDNA remains unactive in the nucleus- template for viral RNA transcription

Dandri, Maura, and Jorg Peterson.*HBV virology*. 8th ed. Hamburg: Medizin Fokus Verlag, 2017.

Serologic Markers of HBV Infection

HBsAg

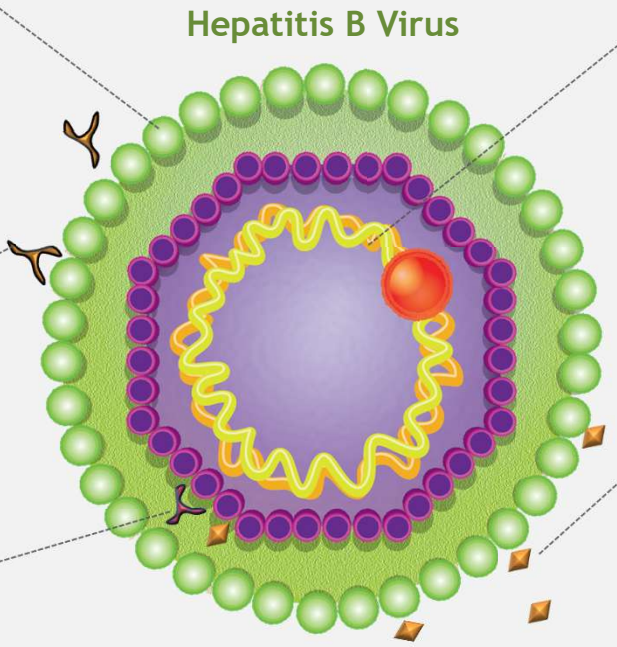
- Hallmark of infection[1]
- Major tool for screening and diagnosis of CHB[2] (if present ≥ 6 months[3])

Anti-HBs

- Antibody to HBsAg[4]
- Marker of recovery and immunity from HBV infection[4]
- In a person with successful immunization, only anti-HBs is detected[4]

Anti-HBc

- Antibody to HBV core antigen[4]
- Marker of prior exposure[4]
  - IgM anti-HBc is a marker of recent or acute infection (4-6 months)[4]



HBV DNA

- Measure of viral load; indicates ongoing viral replication[1]
- Marker of infectivity and risk of major liver disease[2,5]

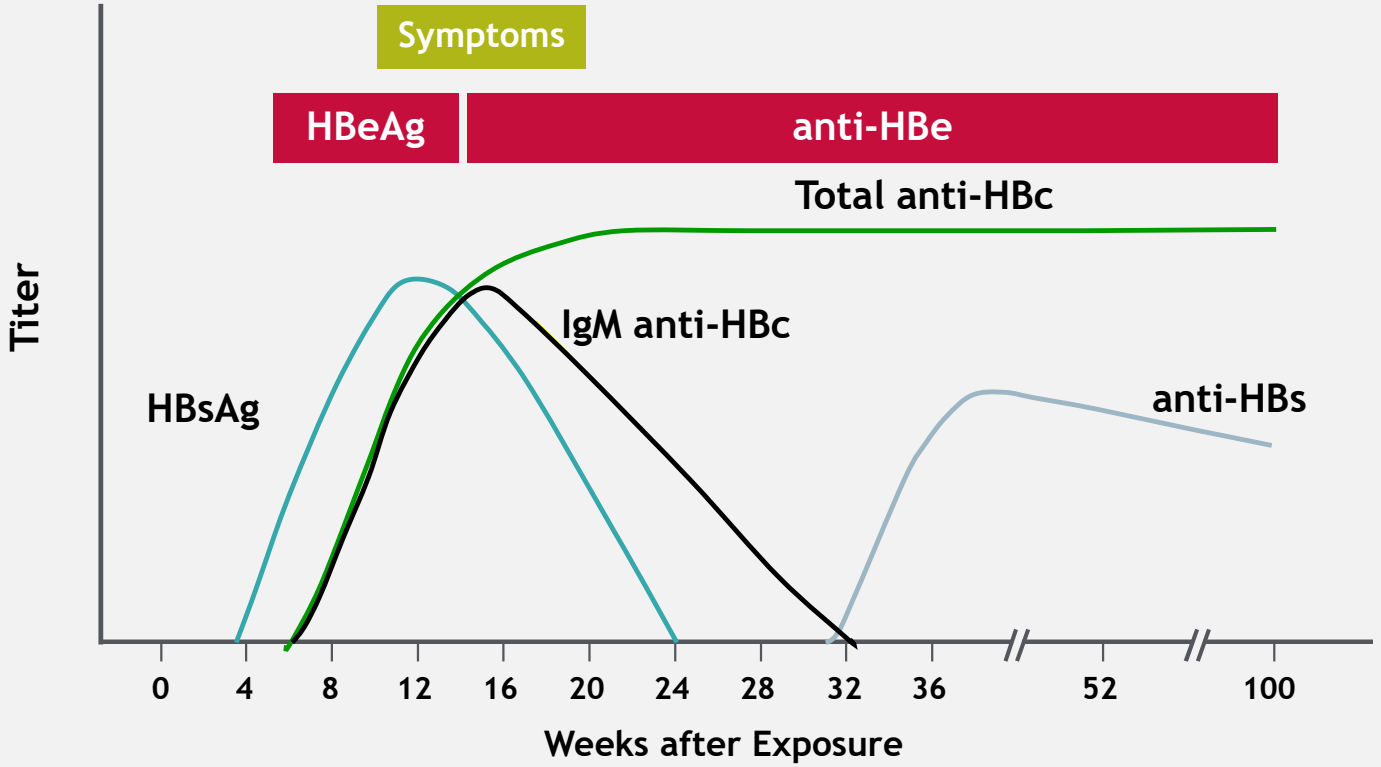
HBeAg

- HBeAg is a viral protein usually associated with active viral replication and may indicate higher infectivity[3,4]

anti-HBs=antibody to HBsAg; anti-HBc=antibody to hepatitis B core antigen; IgM=immunoglobulin M.

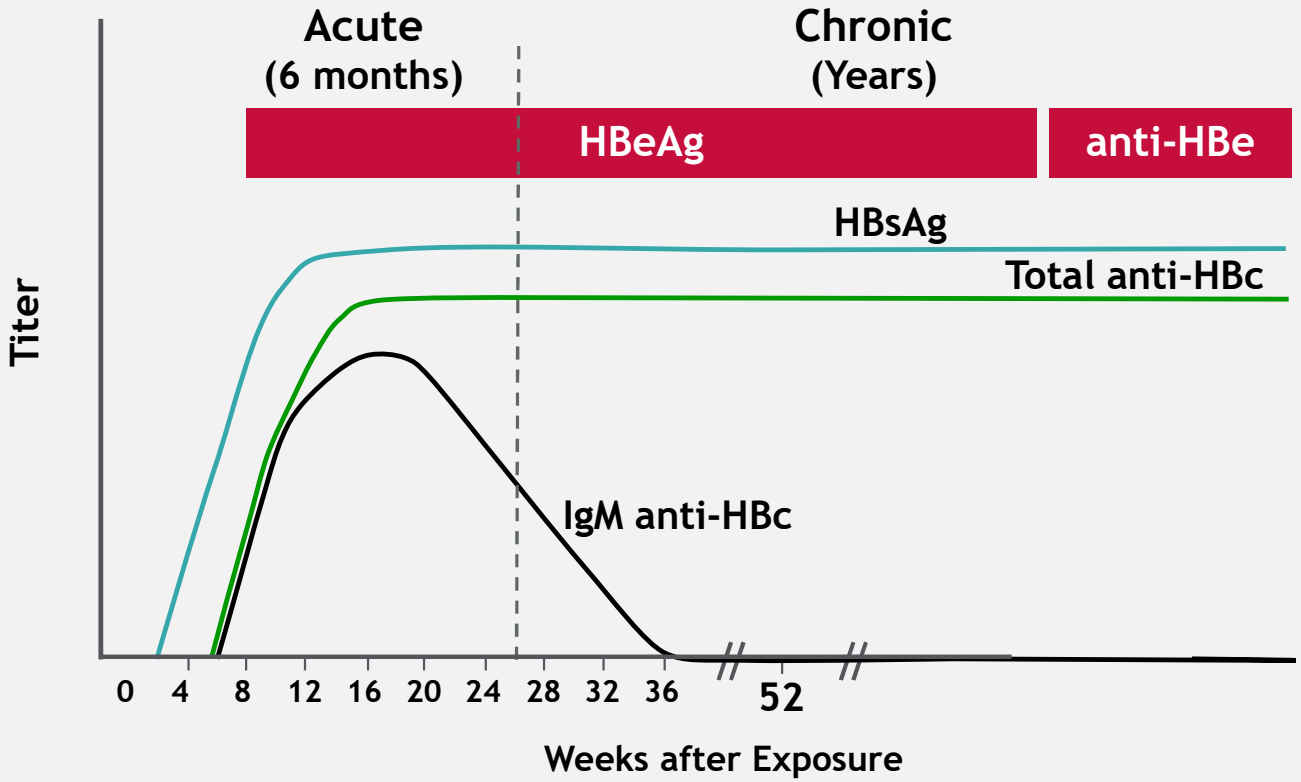
1. Trepo C, et al. *Lancet*. 2014;384:2053-2063; 2. Niederau C. *World J Gastroenterol*. 2014;20:11595-11617; 3. CDC. *Morb Mortal Wkly Rep*. 2008;57:1-20;
4. CDC. *Epidemiology and Prevention of Vaccine - Preventable Diseases*. 13th ed, 2015;
5. Burns GS, Thompson AJ. *Cold Spring Harb Perspect Med*. 2014;4:a024935.

Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course



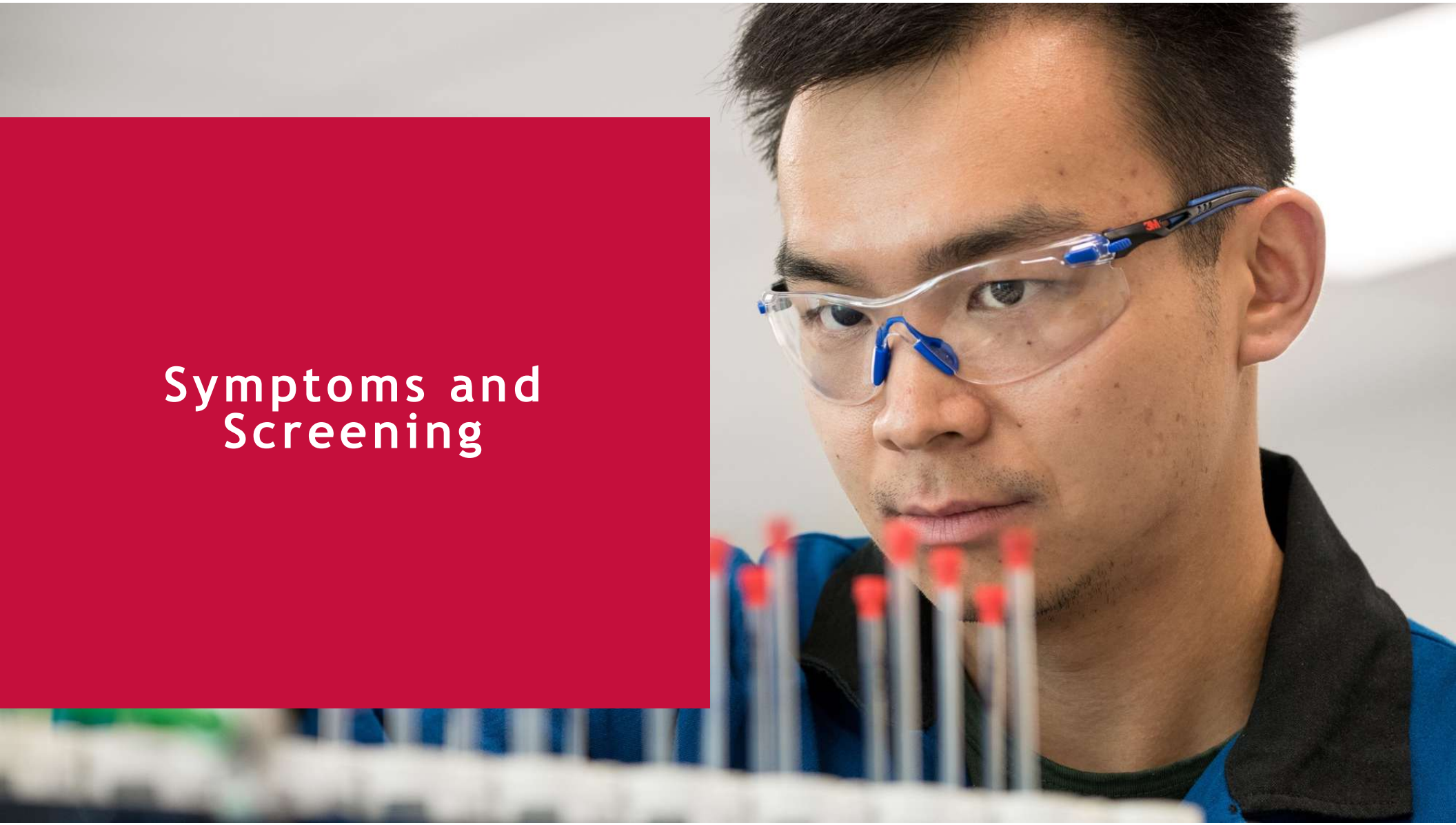
Weinbaum CM, Mast EE, Ward JW. *Hepatology*. 2009;49(5 Suppl):S35-44

Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course



Weinbaum CM, Mast EE, Ward JW. *Hepatology*. 2009;49(5 Suppl):S35-44

Symptoms and Screening



Symptoms of Infection by HBV

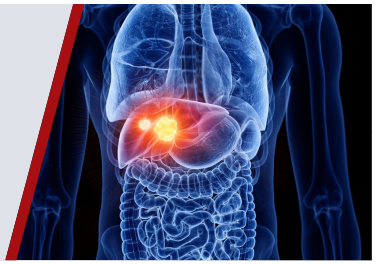
Most people do not experience any symptoms when newly infected.

Some people have acute illness with symptoms that last several weeks:

- Yellowing of the skin and eyes (jaundice)
- Dark urine
- Feeling very tired
- Nausea
- Vomiting
- Pain in the abdomen.

When severe, acute hepatitis can lead to liver failure, which can lead to death.

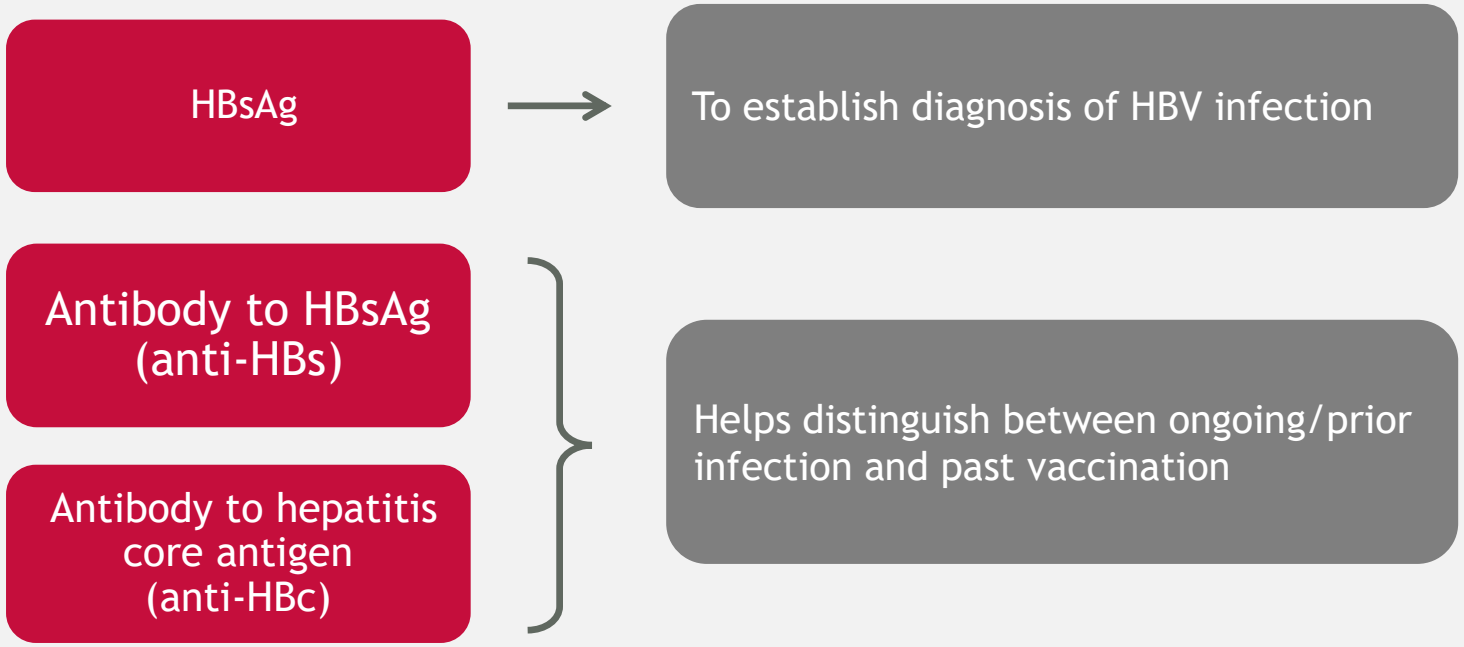
Although most people will recover from acute illness, some people with chronic hepatitis B will develop progressive liver disease and complications like cirrhosis and hepatocellular carcinoma (liver cancer). These diseases can be fatal.



HBV, hepatitis B virus
https://www.who.int/news-room/fact-sheets/detail/hepatitis-b Accessed: April 2025

Recommended Screening Tests

- HBV screening panel



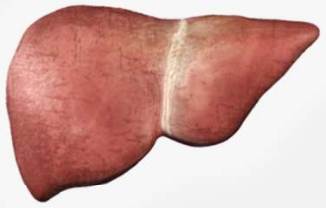
LeFevre ML, et al. *Ann Intern Med*. 2014; 27 May 2014;161(1):58-66

Markers of CHB

- The hallmark of CHB is the presence of **hepatitis B surface antigen (HBsAg)** for > 6 months.
- Other markers of disease may also be present and can help clinicians understand what phase of CHB the patient is in:
- **Levels of HBV DNA**, indicating the level of viral replication
- Levels of **alanine aminotransferase (ALT)**, indicating potential liver injury
- Presence of necroinflammation and liver damage as assessed by **liver biopsy or noninvasive techniques**
- In addition to these markers, clinicians may look at whether the patient is positive or negative for **hepatitis B envelope antigen (HBeAg)**; this is a viral protein that is usually associated with active viral replication and may indicate higher infectivity

Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):661-662.
Trepo C, Chan HL, Lok A. Hepatitis B virus infection. *Lancet*. 2014;384(9959):2053-2063.
WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017.

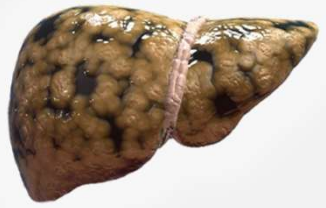
Types of Hepatic Cell Injury Response



Inflammation

Proinflammatory cells – hepatitis

Most hepatic injury involves necrosis (cell death) and inflammation

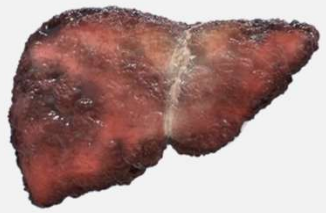


Degeneration

Ballooning degeneration - water

Feathery degeneration - bile

Steatosis (“fatty liver”) - lipids



Fibrosis

Characterized by

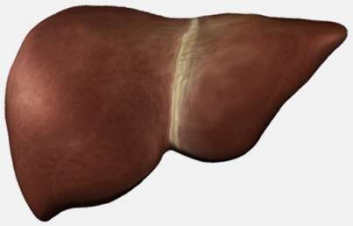
- Deposition of collagen
- Formation of fibrous tissue within the liver

Often occurs in response to inflammation/direct toxic injury to liver

Over time, bridging fibrosis may occur

Kumar V,et al, eds. *Robbins and Cotran Pathologic Basis of Disease, Professional Edition*. 8th Ed. Philadelphia, PA: Saunders, an imprint of Elsevier; 2010. Chapter 16. Page 3 of PDF, para 3.
Ismail MH, et al. *The Saudi Journal of Gastroenterology*. 2009; 15(1): 72-79. Page 1 of PDF, col 1, para 1.
Fallowfield JA, et al. *Clin Liver Dis*. 2006; 10: 481-497. Page 2 of PDF, para 2.

Types of Hepatic Cell Injury Response



Necrosis

Frequently described by the pattern of hepatocellular death within the lobule or by how much tissue is involved

Pattern of Necrosis	Description(s)
Centrilobular	• Found in the region near a central hepatic vein • Most common type observed
Focal	• Limited to scattered cells within lobules
Piecemeal (or interface hepatitis)	• Inflammation extends from the portal tract into the hepatic parenchyma
Submassive	• Involves multiple contiguous lobules
Bridging	• Characterized by bands of dead hepatocytes that stretch between adjacent portal triads and/or central veins
Massive	• Involves most of the liver

"necrosis." *Stedman's Medical Dictionary*. 27th Ed. 2000. Lippincott Williams & Wilkins: Baltimore, MD. Page 3, col 1, para 15.
Kumar V, et al.eds. *Robbins and Cotran Pathologic Basis of Disease, Professional Edition*. 8th Ed. Philadelphia, PA: Saunders, an imprint of Elsevier; 2010. Chapter 16. Page 3 of PDF, para 4.
Angulo P, et al, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Ed. Philadelphia, PA: Saunders, an imprint of Elsevier; 2010. Chapter 89. Page 5 of PDF, col 1, para 1.

Types of Hepatic Cell Injury Response

End-stage form of liver disease

Decompensated

- **Extensively scarred**
- Unable to function adequately
- Patients develop symptoms and experience life-threatening complications

Compensated

- **Heavily scarred**
- Still able to carry out important bodily functions
- Patients may live many years with no symptoms

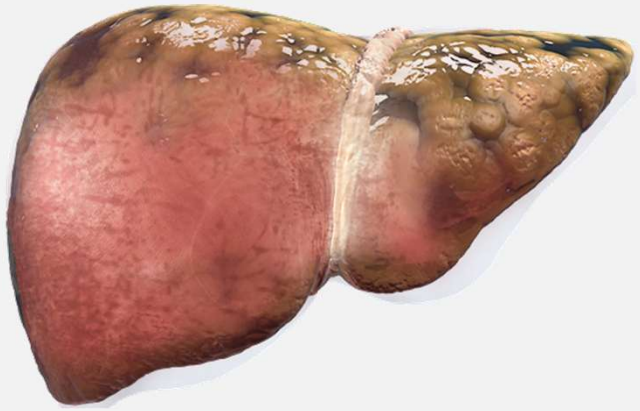
Potential Symptoms

- Ascites
- Upper GI bleeding
- Hepatorenal syndrome
- Hepatic encephalopathy

Kumar V, et al eds. *Robbins and Cotran Pathologic Basis of Disease, Professional Edition*. 8th Ed. Philadelphia, PA: Saunders, an imprint of Elsevier; 2010. Chapter 16. Page 3 of PDF, para 8.
Franciscus A. What is Cirrhosis? Available at: http://www.hcvadvocate.org/hepatitis/factsheets_pdf/cirrhosis.pdf. Accessed July 2012. Page 1 of PDF, last paragraph; Page 2 of PDF, col 1, para 1-2.

Regeneration

As little as 25% of a liver can regenerate into a whole liver.



- Accomplished by rapid cell divisions and tissue mass replacement
- Occurs following injury due to chronic hepatitis, hepatotoxic reactions, surgery, and transplantation

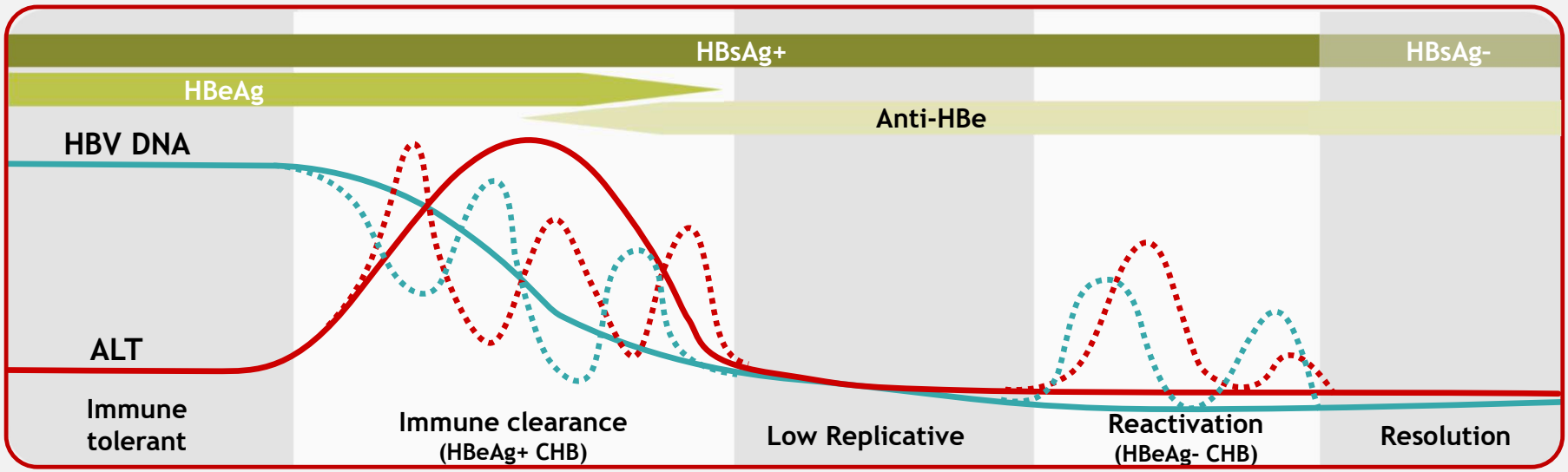
Repeated regeneration cycles in chronic hepatitis may result in genetic errors in hepatocytes, which may be responsible for HCC development

HCC, hepatocellular carcinoma

Bergmann A, et al. *Sci Signal*. 2010; 3(145). Page 2 of PDF, para 3.
NIH. A Report of the Liver Disease Subcommittee of the Digestive Diseases Interagency Coordinating Committee. *Action Plan for Liver Disease Research*. NIH Publication No. 04-5491. 2004. Chapter 3. Available at: http://www2.niddk.nih.gov/NR/rdonlyres/EBC2BEE1-76B1-4F03-8D53-960A04F412A0/0/ldrb_chapter3.pdf. Accessed July 2012. Page 2 of PDF, col 1, para 1; col 2, para 2-3.
Leong TYM, et al. *HPB*. 2005; 7: 5-15. Page 1 of PDF, abstract.

The Four Phases of Chronic Hepatitis B

Course of Chronic Hepatitis B Infection



- This phase occurs in patients with perinatally acquired infection
- Minimal or no inflammation
- May last 1 to 4 decades

- High or fluctuating HBV DNA levels
- Persistent or intermittent fluctuation in ALT levels
- Active inflammation and liver damage

- Low or undetectable HBV DNA levels
- Normal ALT levels
- Mild hepatitis, minimal fibrosis, but cirrhosis may be present from previous liver damage

- Some patients may have reactivation of HBV replication
- Usually older patients with more advanced liver disease
- Fluctuating levels of ALT and HBV DNA

- After many years, some patients may enter a resolution phase
- Not considered a "cure" as intra-cellular HBV DNA is still present

CHB follows a nonlinear clinical course; not all patients will go through each phase

Keeffe EB et al. *Gastroenterol Hepatol*. 2008;6:1315-1341.
Yim HJ, Lok ASF. *Hepatology*. 2006;43:S173-S181.
Martin P, et al. *Clin Gastroenterol Hepatol*. 2015 July 15.

Current Treatment Guidelines

Updated 2024 WHO HBV Guidelines

Provide 4 options for meeting treatment eligibility that will capture a much higher proportion (at least 50%) of all HBsAg-positive people versus about 8–15%

New APRI criteria for staging liver disease

Alternative antiviral regimens for treatment

- TDF or entecavir preferred first-line regimens
- TDF + lamivudine (3TC) or TDF + emtricitabine (FTC) if TDF monotherapy not available
- Tenofovir alafenamide (TAF) recommended for people with established osteoporosis and/or impaired kidney function

Expand access to antiviral prophylaxis for HBsAg positive pregnant women

- TDF prophylaxis: All HBsAg-positive pregnant women if lack of access to HBV DNA assays

Use of point-of-care HBV DNA assays

Reflex Hepatitis D co-infection testing

Recommendations: Non-invasive testing for Fibrosis

Updated recommendation:

- **APRI (aspartate aminotransferase-to-platelet ratio index)** is recommended as the **preferred non-invasive test** to assess for the **presence of significant fibrosis or cirrhosis** among adults in resource-limited settings.
- **Transient elastography (FibroScan®)** may be a preferable non-invasive test in settings where it is available and cost is not a major constraint.

(strong recommendation, moderate-certainty evidence)

New recommendation:

- **Evidence of significant fibrosis (≥F2)** should be based on **an APRI score of >0.5** or **transient elastography value of >7.0 kPa**, and **cirrhosis (F4)** should be based on clinical criteria (or an **APRI score of >1.0** or) **transient elastography value of >12.5 kPa**.

(adults: strong recommendation, moderate-certainty evidence; adolescents: strong recommendation, low-certainty evidence)

TABLE 4.1 METAVIR liver-biopsy scoring system

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

APRI = (AST/ULN) X 100/platelet count

Diagnosing ≥ F2 fibrosis, APRI score >0.5

- Sensitivity: 71.7% (67.1–75.8%)
- Specificity: 64.8% (58.6–70.5%)

Diagnosing cirrhosis: APRI score >1.0

- Sensitivity 54.3% (47.7–60.8%)
- Specificity 76.9% (71.7–81.4%)

World Health Organization

Recommendations: Who to Treat?

Treatment is recommended for all adults and adolescents (aged ≥12 years) with CHB (including pregnant women and girls and women of reproductive age) with:

1. **Evidence of significant fibrosis** (≥F2) based on **APRI score of >0.5 or transient elastography value of >7 kPa** or evidence of **cirrhosis (F4) (based on clinical criteria or APRI score of >1 or transient elastography value of >12.5 kPa[c]),** *regardless of HBV DNA or ALT levels. (Adults: Strong/Mod, Adolescents Strong/Low)* — **20-25% of HBsAg +ve**

OR

2. **HBV DNA >2000 IU/mL and an ALT level above upper limit of normal** (ULN) (**30 U/L for men and boys & 19 U/L for women and girls**). For adolescents, this should be based on ALT>ULN on at least two occasions in a 6- to 12-month period. *(Adults: Strong/high; [HBV DNA >20 000 IU/mL] & Low [HBV DNA 2000–20 000]; Adolescents: Conditional/Low)* — **20-35% of HBsAg +ve**

OR

3. **Presence of coinfections** (such as HIV, hepatitis D or hepatitis C); **family history of liver cancer or cirrhosis; immune suppression; comorbidities** (such as metabolic dysfunction-associated steatotic liver disease); **or extrahepatic manifestations**, *regardless of the APRI score or HBV DNA or ALT levels. (Adults: Strong/Mod; Adolescents: Conditional/Low)* — **5-8% of HBsAg +ve**

OR

4. **In the absence of access to an HBV DNA assay:**
Persistently abnormal ALT levels (defined as **two ALT values >ULN at unspecified intervals during a 6- to 12-month period**), *regardless of APRI score. (Adults and adolescents: Conditional/very Low)* — **20% of HBsAg +ve**

WHO. Global hepatitis report 2024: action for access in low- and middleincome countries. 2024. Available from: https://www.who.int/publications/i/ item/9789240091672

Summary of Preferred and alternative first-line antiviral regimens

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adults	TDF ETV	TDF + 3TC TDF + FTC (where TDF monotherapy is not available)	ETV TAF (for people with established osteoporosis and/or impaired kidney function)
Adolescents (12-17 years)	TDF ETV	TDF + 3TC TDF + FTC where TDF monotherapy is not available) TAF	
Children (2-11 years)	TDF* ETV		

TDF: tenofovir disoproxil fumarate; ETV: entecavir; 3TC: lamivudine; FTC: emtricitabine; TAF: tenofovir alafenamide fumarate.

*Low dose formulations of TDF may not be widely available

Key benefits of all recommended nucleos(t)ide analogues (TDF, ETC, TDF + 3TC or FTC, ETV and TAF):

- TDF, TDF + 3TC or TDF + FTC, ETV and TAF are all potent inhibitors of HBV replication, and, based on data from reported systematic reviews, are all highly effective in reducing disease progression. HBeAg seroconversion (among HBeAg-positive people) occurs in the minority (10–15% per year), and HBsAg loss is infrequent.
- All the drugs have a high genetic barrier to resistance and very low observed rates of drug resistance over long-term (five-year) follow-up. However, resistance to ETV occurs frequently among people with 3TC resistance, which can limit its use in settings where 3TC has been previously widely prescribed.
- The recommended first-line regimens (TDF, TDF + 3TC or TDF + FTC and ETV) can be used across all age groups – adults, adolescents and children down to two years (based on FDA and EMA regulatory approval).

WHO. Global hepatitis report 2024: action for access in low- and middleincome countries. 2024. Available from: https://www.who.int/publications/i/ item/9789240091672.

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)

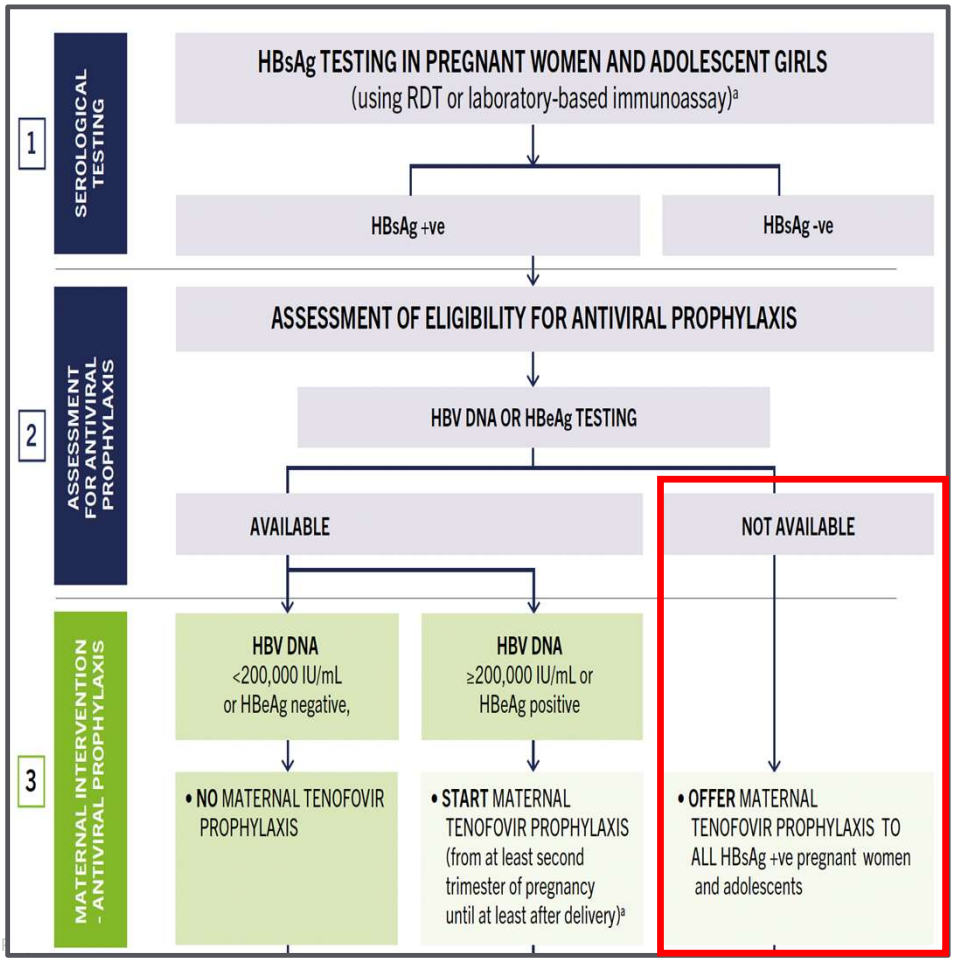
New 2024 recommendation

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.



Preventing mother-to-child transmission of hepatitis B using antiviral prophylaxis

Immunization

a) All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferable within 24 hours.

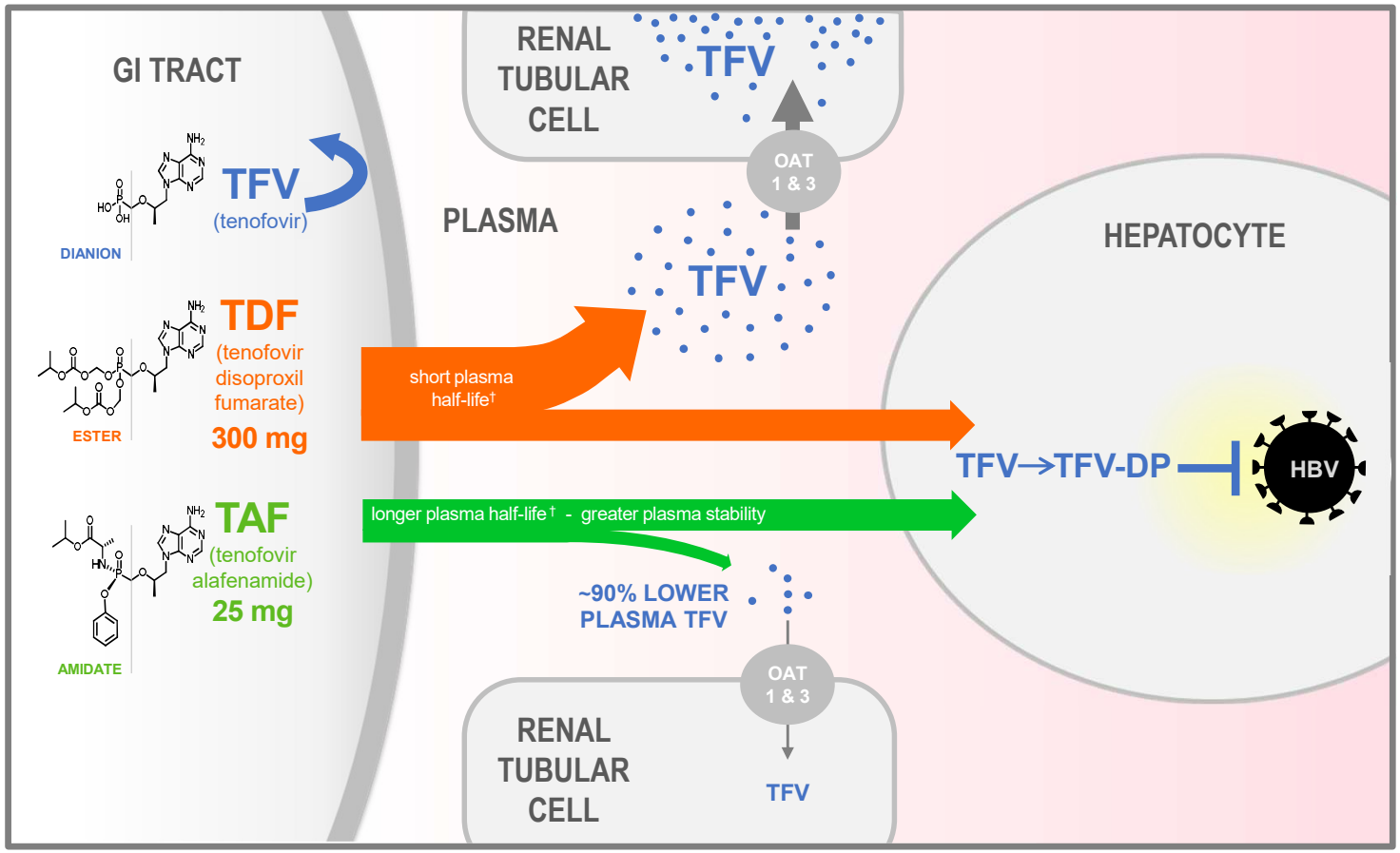
b) Delivery of hepatitis B vaccine within 24 hours of birth should be a performance indicator for all immunization programmes, and reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.

c) The birth dose should be followed by two or three additional doses to complete the primary immunization series.

WHO. Global hepatitis report 2024: action for access in low- and middleincome countries. 2024. Available from: https://www.who.int/publications/i/ item/9789240091672.

‡ ‡

TAF – A Novel Prodrug of Tenofovir

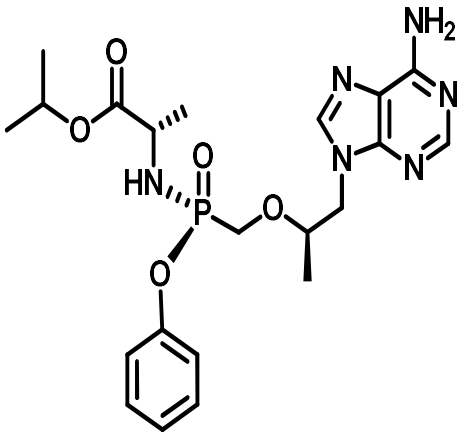


† $T_{1/2}$ based on *in vitro* plasma data - TDF = 0.4 minutes, TAF = 90 minutes.

Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. Birkus G et al. *Antimicr Agents Chemo* 2007;51(2):543-550. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66. Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. Sax P, et al. *JAIDS* 2014. 2014 Sep 1;67(1):52-8. Sax P, et al. *Lancet* 2015. Jun 27;385(9987):2606-15. Agarwal K et al. *J Hepatology* 2015; 62: 533-540; Buti EASL 2016, Oral GS06; Chan, EASL 2016, Oral GS12

TAF Highlights and Key Attributes

TAF Nucleotide Analog

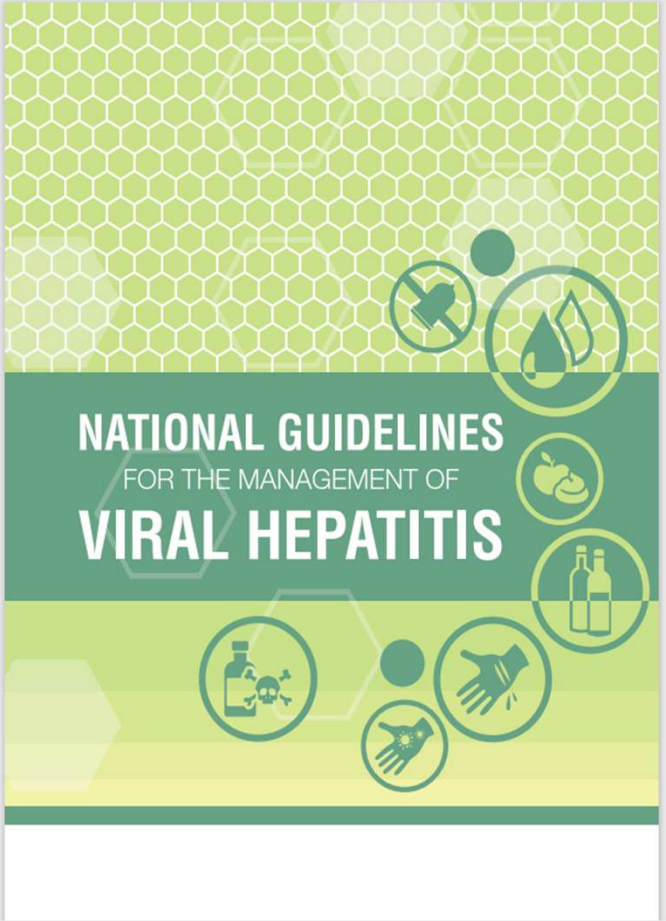


- **Tenofovir Alafenamide (TAF)**
  - Novel prodrug of tenofovir (TFV)
  - More stable in plasma with roughly 90% reduction in circulating TFV level vs TDF
  - Once-daily, oral, 25 mg tablet with food
  - Less effects on various bone and renal parameters vs TDF

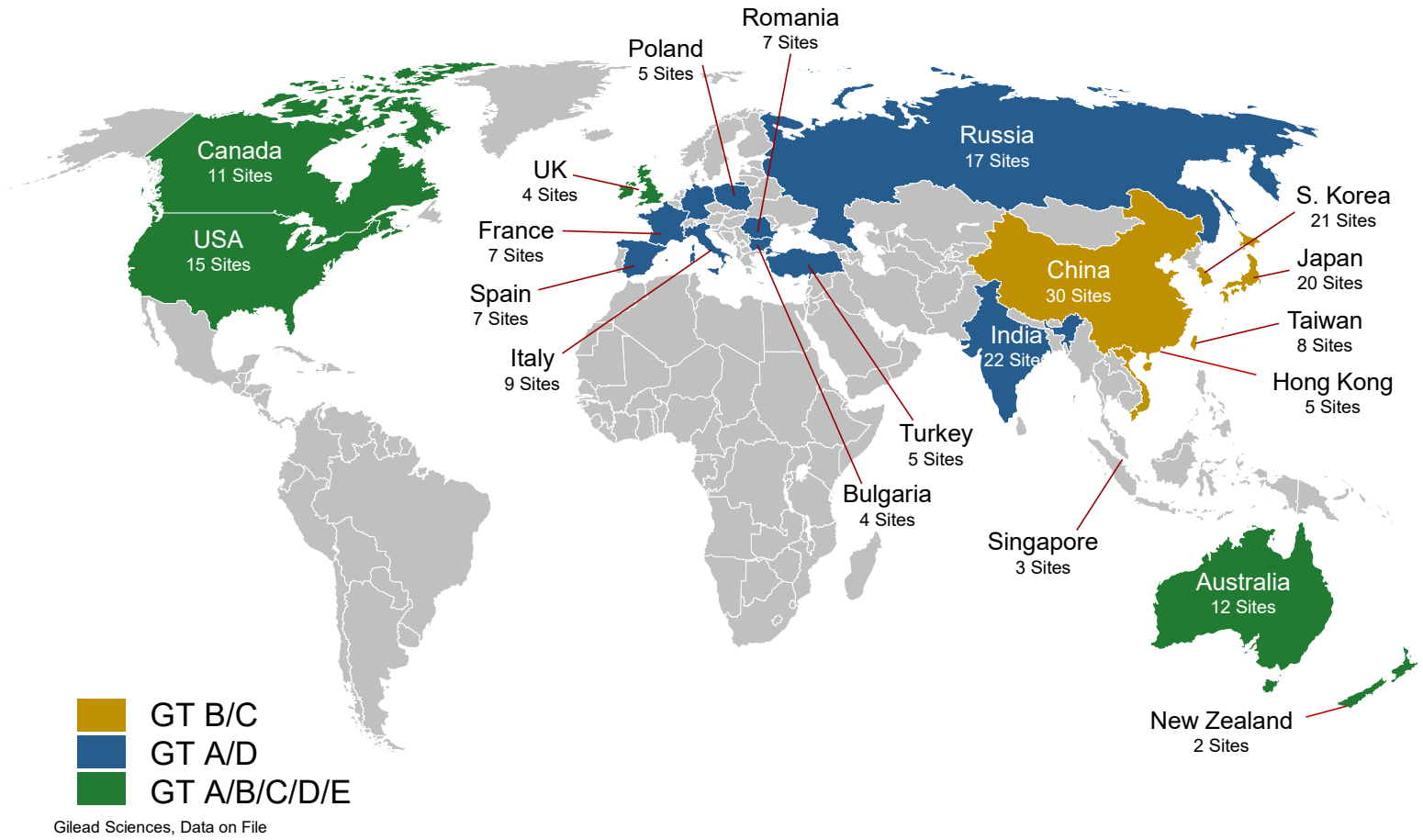
Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. Birkus G et al. *Antimicr Agents Chemo* 2007;51(2):543-550. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66. Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. Sax P, et al. *JAIDS* 2014. 2014 Sep 1;67(1):52-8. Sax P, et al. *Lancet* 2015. Jun 27;385(9987):2606-15. Agarwal K et al. *J Hepatology* 2015; 62: 533-540; Buti EASL 2016, Oral GS06; Chan, EASL 2016, Oral GS12

National Guidelines- page 40

Nucleos(t)ide analogue options for chronic HBV and dosage regimens33,34,48,49,54	
TDF	• recommended dosage for adults with normal renal function (creatinine clearance >50 ml/min): 300 mg per day • dosage reduction necessary in patients with impaired renal function
TAF	• adults or adolescents (aged ≥12 years and ≥35 kg body weight) • dosage : 25mg daily • recommended in individuals >60 years • recommended for adults with impaired renal function - eGFR <60ml/min/1.73m2 - albuminuria >30 mg/24 hrs or moderate dipstix proteinuria - hhaemodialysis - low phosphate • recommended in adults with bone disease - chronic steroid use - osteoporosis - history of fragilty fracture • requires Section 21 application to SAHPRA
Entecavir	• recommended dosage for adults with normal renal function: eGFR >50 ml/min - 0.5mg daily if Lamivudine naïve 1mg daily if previously exposed to Lamivudine or if Lamivudine refractory or resistant * • dosage reduction necessary in patients with impaired renal function **
Lamivudine	• recommended dosage for adults with normal renal function: 100 mg/day (creatinine clearance >50 ml/min) • HIV/HBV co-infection: 300mg Lamivudine daily61 • recommended dosage for children: 3 mg/kg/day, maximum dosage 100 mg/day • dosage reduction necessary in patients with impaired renal function • recommended in unstable patients with renal impairment – resistance 20per cent at six months61, if Entecavir or TAF not available



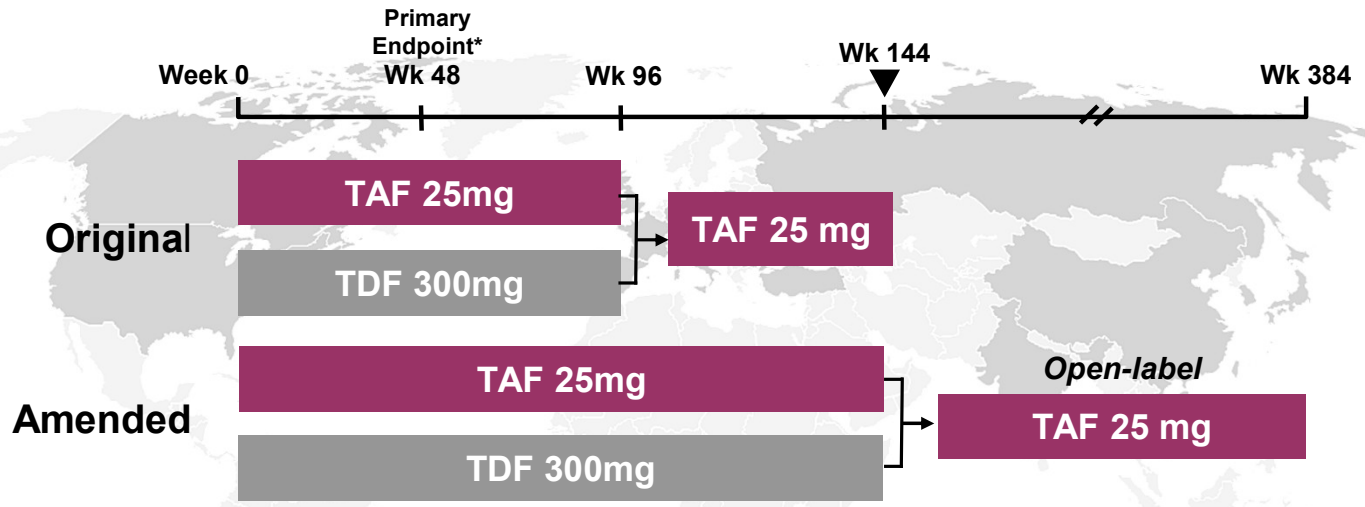
TAF Phase 3 Program: 191 sites, 19 countries, 1298 patients (GS-US-320-0108 and GS-US-320-0110)



Gilead Sciences, Data on File

‡

Original and Amended Study Designs for 108 and 110



- Two Phase 3, randomized, double-blind, active-controlled trials
  - Study 108 (N=425): HBeAg-negative patients
  - Study 110 (N=873): HBeAg-positive patients
- Key inclusion criteria (both studies)
  - HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males) >38 U/L (females); eGFR ≥50 mL/min
- 2:1 randomization
  - Stratified by HBV DNA level and treatment status (naïve/experienced)

‡

Baseline Demographics

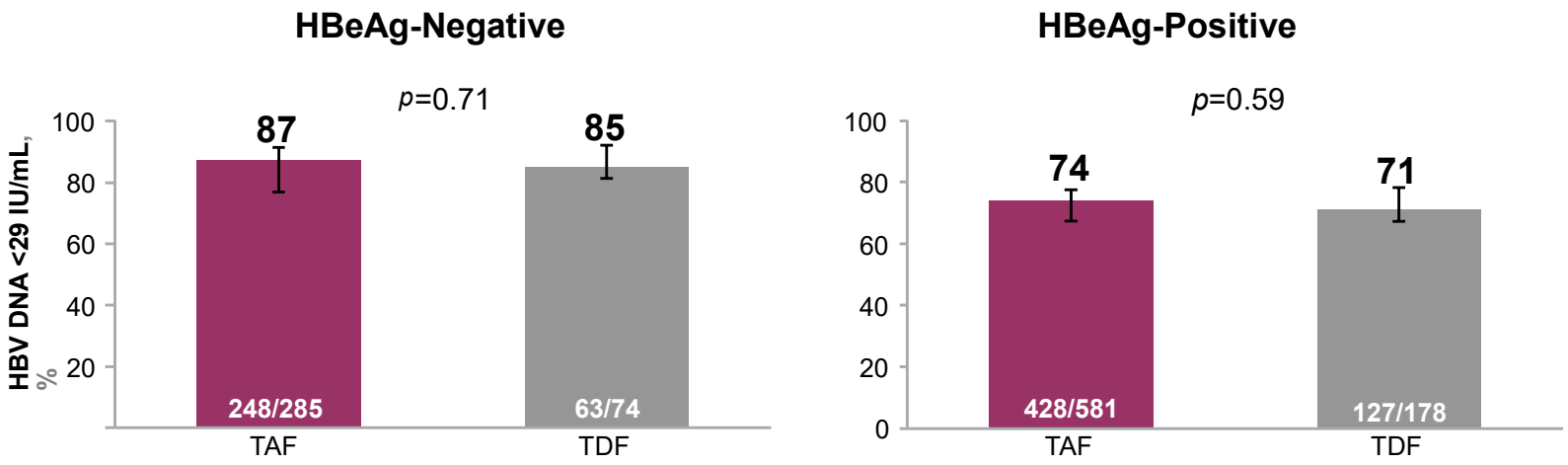
		TAF n=866	TDF n=252
Median age, y (range)		40 (18–80)	41 (18–72)
Male, n (%)		544 (63)	164 (65)
Asian, n (%)		687 (79)	187 (74)
Mean body mass index, kg/m^2 (SD)		24 (4)	24 (4)
Nucleos(t)ide experienced, n (%)		211 (24)	65 (26)
HBV genotype, n (%)	A	54 (6)	20 (8)
	B	160 (18)	39 (15)
	C	418 (48)	120 (48)
	D	224 (26)	69 (27)
Mean HBV DNA, $\log_{10}$ IU/mL (SD)		7.0 (1.59)	7.1 (1.62)
Median ALT, U/L (Q1, Q3)		80 (56, 123)	80 (51, 126)
FibroTest score ≥0.75, n (%)		76 (9)	30 (12)
HBeAg positive, n (%)		569 (66)	176 (70)

There were no statistical differences between the two groups for the parameters listed above

Chan, AASLD 2018, 0381

‡

HBV DNA <29 IU/mL at Week 144 (ITT)



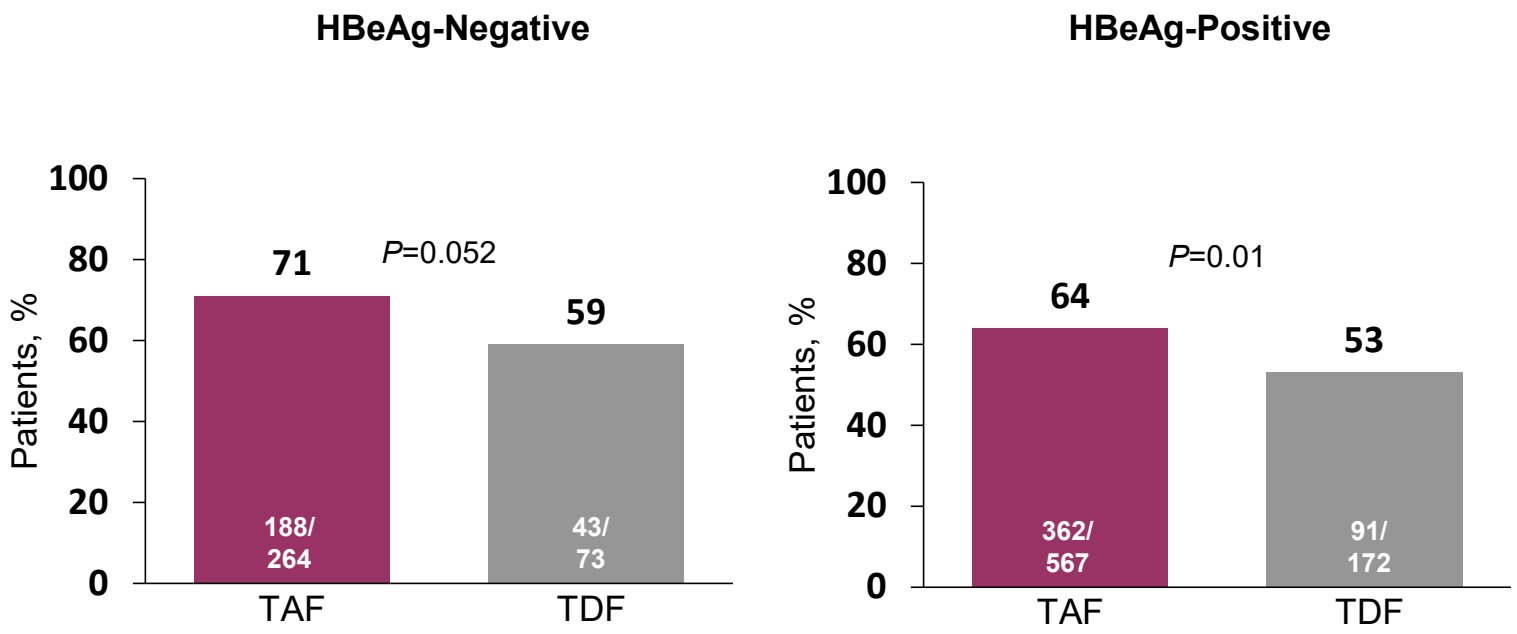
	TAF	TDF
HBeAg loss, n/N (%)	135/565 (24)	39/175 (22)
HBeAg seroconversion, n/N (%)	105/565 (19)	23/175 (13)
HBsAg loss, n/N (%)	9/857 (1)	3/251 (1)
HBsAg seroconversion, n/N (%)	2/857 (<1)	0/251 (0)

No resistance to TAF and TDF was detected through Week 144

Chan, AASLD 2018, 0381 and 0386

‡

ALT Normalization (AASLD 2018 Criteria) at Week 144



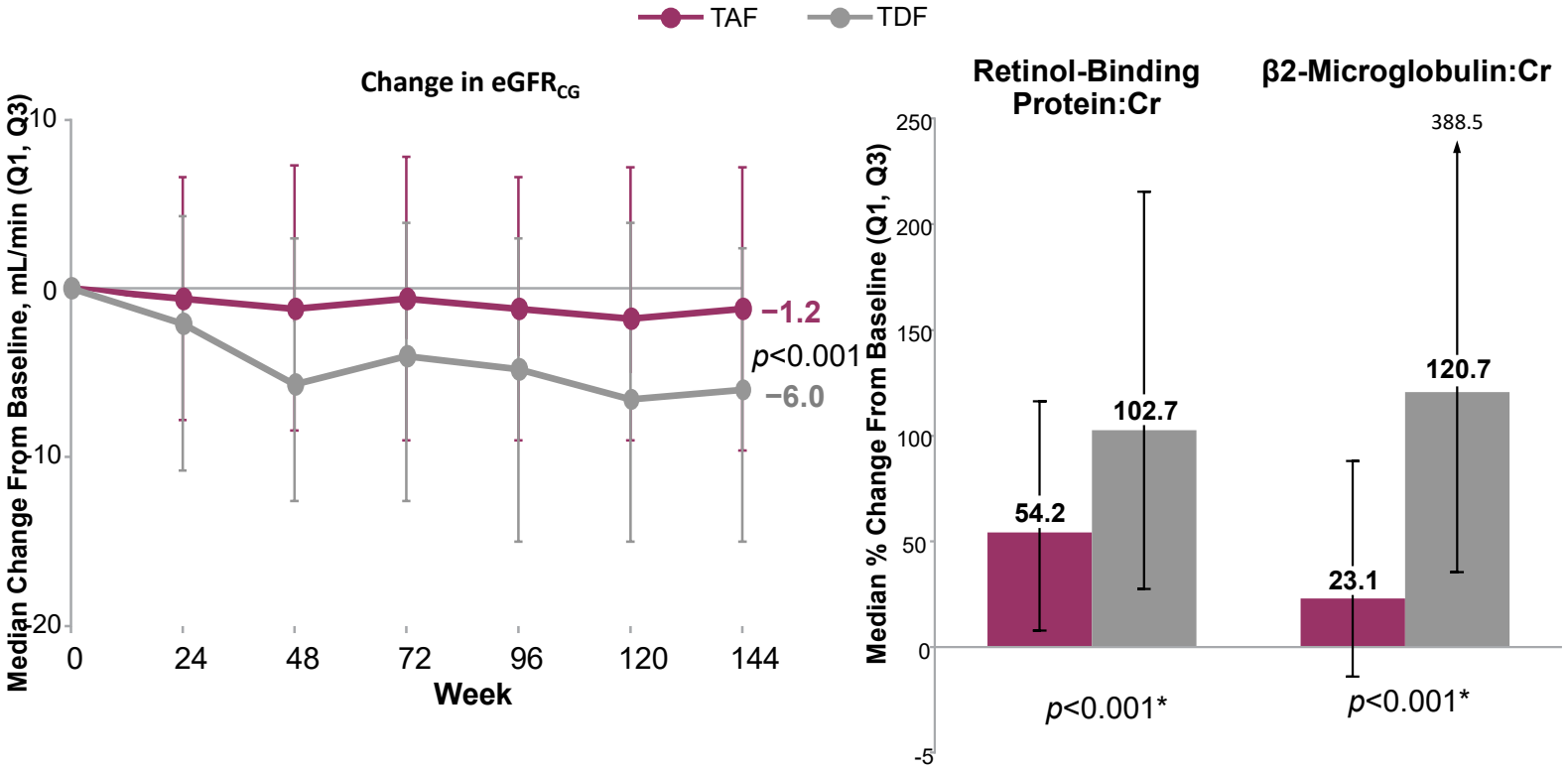
There were higher rates of ALT normalization by AASLD 2018 criteria in patients on TAF compared to TDF

AASLD 2018 criteria ULN: males ≤ 35 U/L, females ≤ 25 U/L

Chan, AASLD 2018, 0381

‡

Change in Renal Parameters Over 144 Weeks



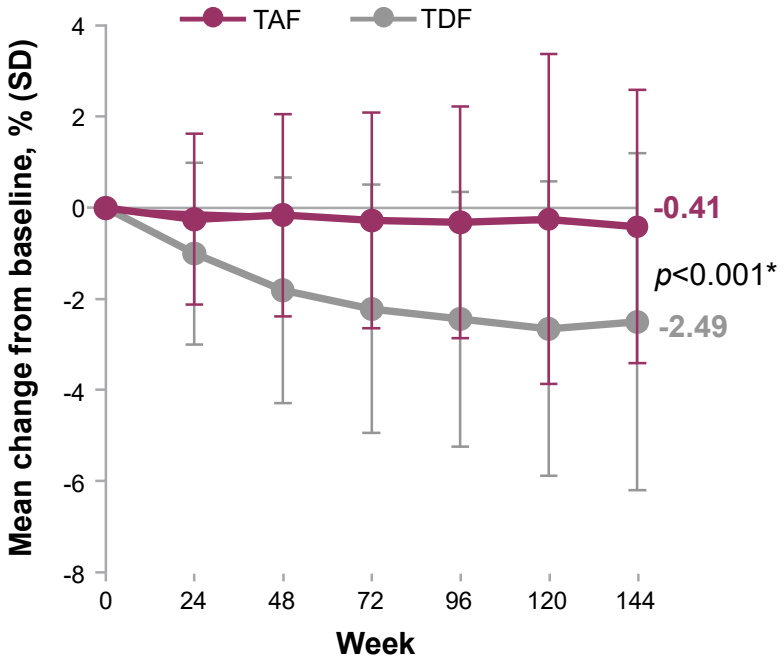
There were significantly smaller decreases in eGFR$_{CG}$ and smaller changes in proximal tubular markers with TAF compared to TDF at Week 144

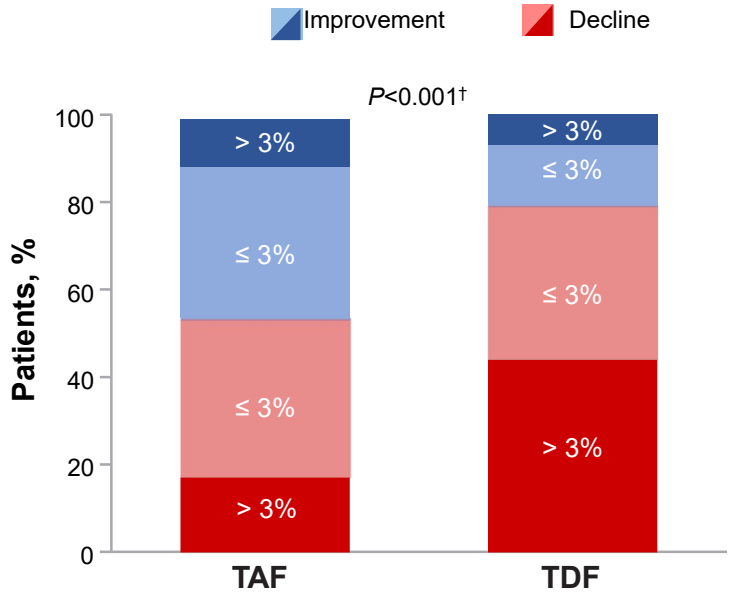
*From 2-sided Wilcoxon rank-sum test

Chan, AASLD 2018, 0381

Changes in Bone Mineral Density (BMD) in Patients Over 144 Weeks

Hip





There were significantly less declines in hip BMD in patients on TAF compared to TDF

*From analysis of variance model including treatment as fixed effect
† From Cochran-Mantel-Haenszel test for ordinal data (row mean scores differ statistic was used).

Chan, AASLD 2018, 0381