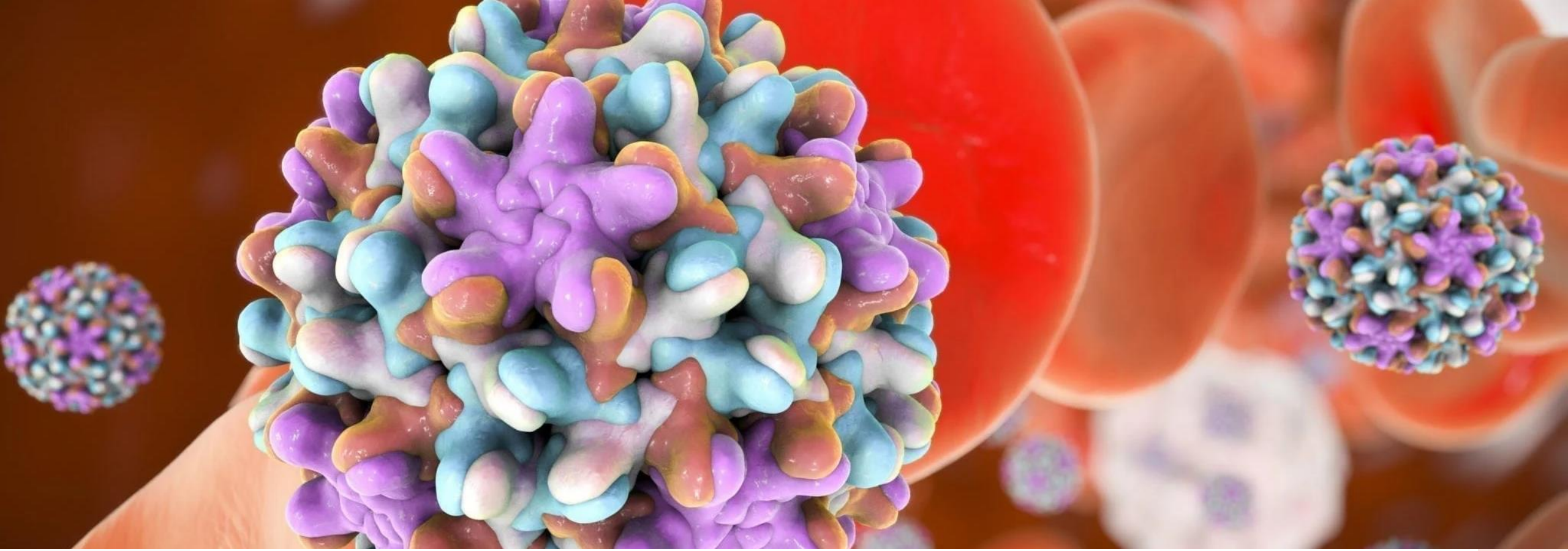


HEPATITIS B

Presenter: Isneen Hilmy

Facilitator: Prof Wendy Spearman

Project ECHO® Gastroenterology Foundation of sub Saharan Africa

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

Monday, January 16th, 2023

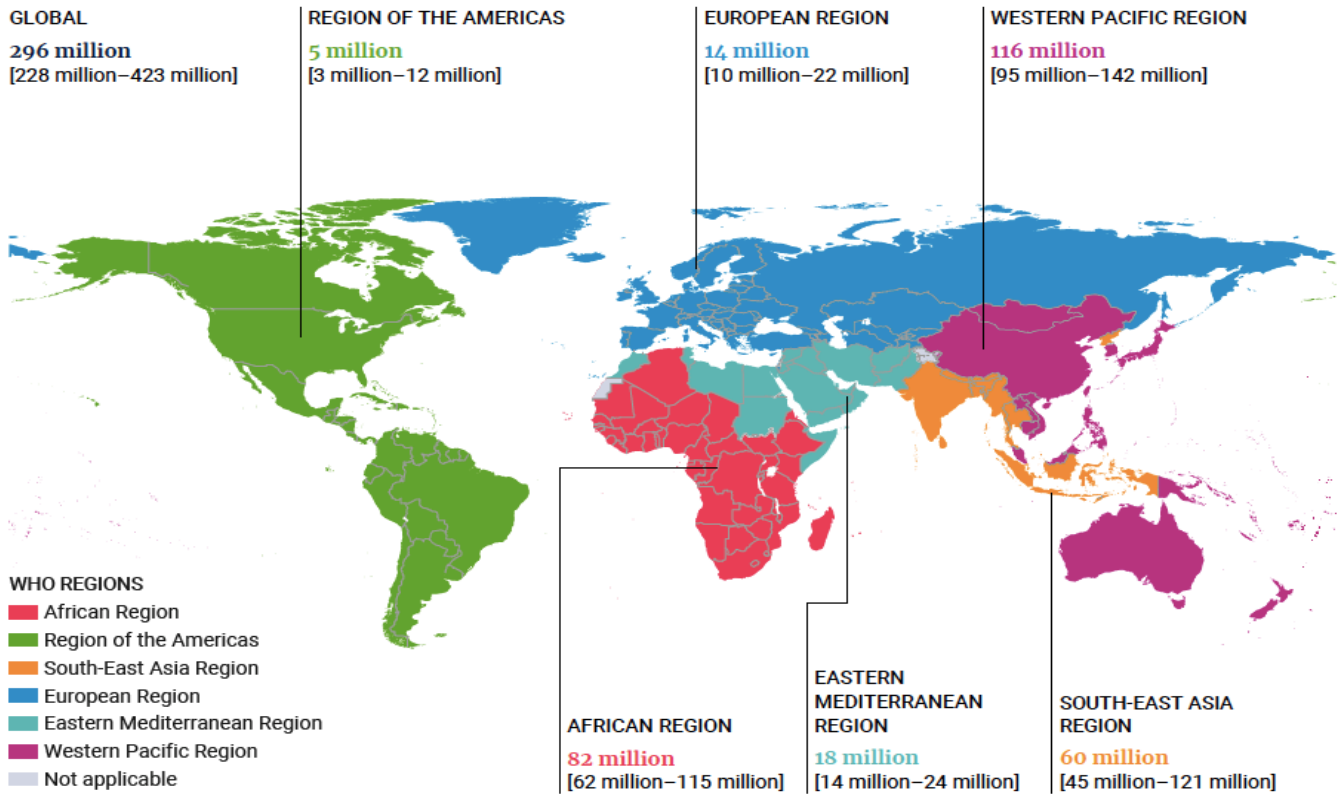
Global Prevalence

296 million people were living with chronic hepatitis B infection in 2019

Infection is highest in the Western Pacific Region and the WHO African Region, where 116 million and 81 million people

1.5 million new infections each year.

In 2019, hepatitis B resulted in an estimated 820 000 deaths, mostly d/t CoL & HCC (primary liver cancer).



Sub-Saharan Africa and South Africa

In Africa → approx. 82 million have CHB

HBV related deaths in sub-Saharan Africa is estimated to be 87,890 annually.

Numerous reports shows high incidence (41.2 per 100,000 people per year) of HCC in sub-Saharan Africa and 80% of HCC is due to HBV infection

Approximately 2.5 million in South Africa

South African HBsAg prevalence in adults ranges from 3% to 25%

Hepatitis B vaccine was introduced into the vaccination schedule in SA in 04/1995

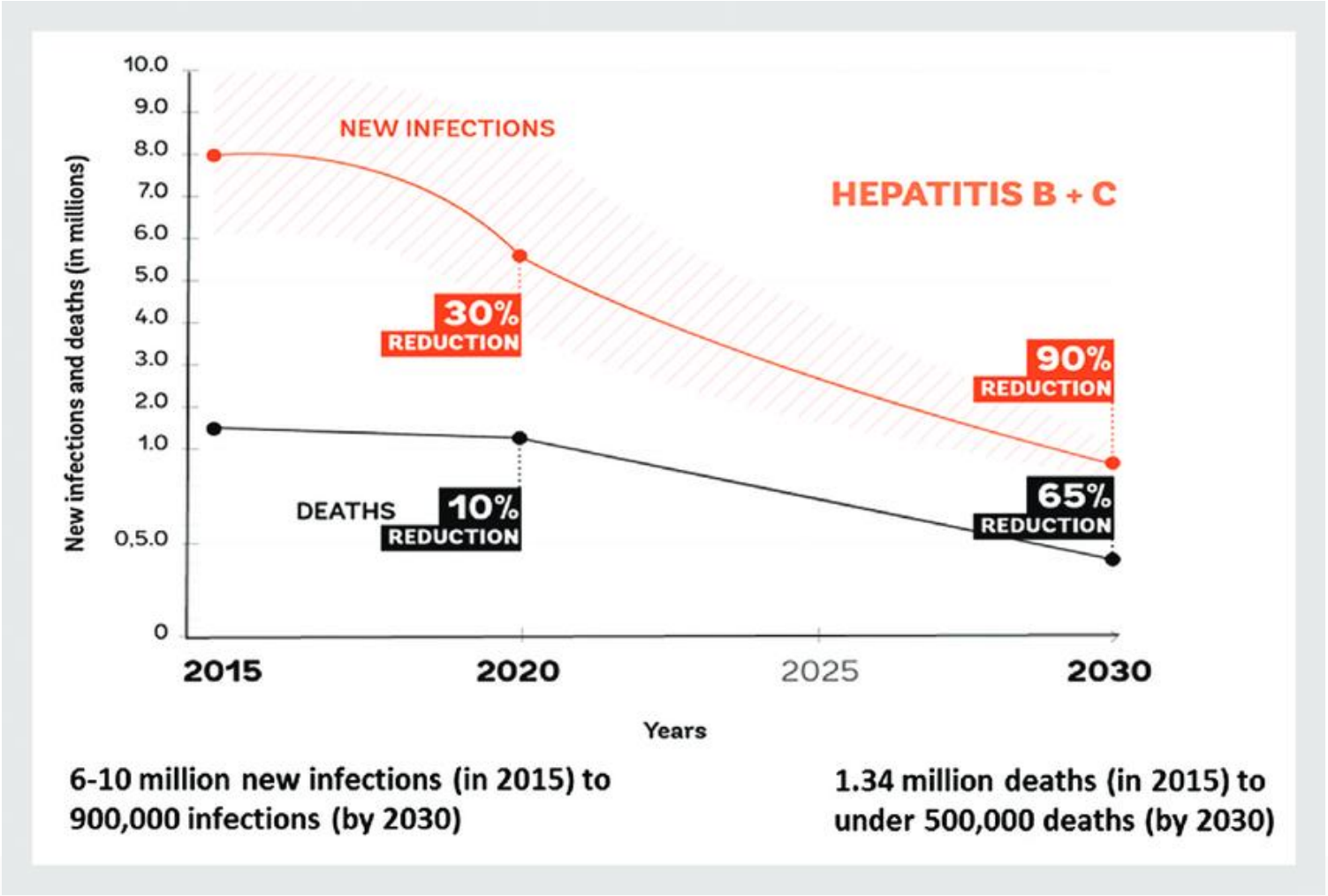
- Overall seroprevalence of HBsAg declining from 12.8 % to 3% in some studies in the pre-HIV era.

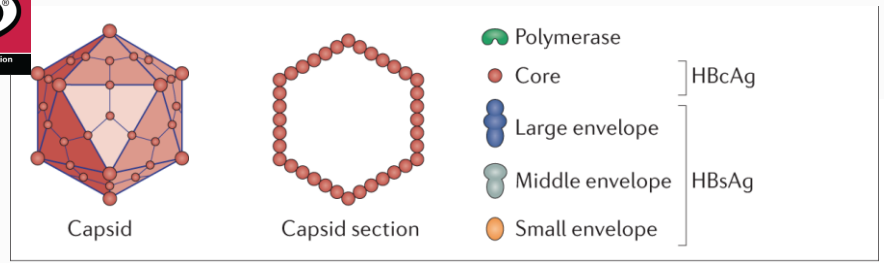
Spearman CW, Afihene M, Ally R, Apica B, Awuku Y, Cunha L, Dusheiko G, Gogela N, Kassianides C, Kew M, Lam P, Lesi O, Lohouès-Kouacou MJ, Mbaye PS, Musabeyezu E, Musau B, Ojo O, Rwegasha J, Scholz B, Shewaye AB, Tzeuton C, Sonderup MW; Gastroenterology and Hepatology Association of sub-Saharan Africa (GHASSA). Hepatitis B in sub-Saharan Africa: strategies to achieve the 2030 elimination targets. Lancet Gastroenterol Hepatol. 2017 Dec;2(12):900-909. doi: 10.1016/S2468-1253(17)30295-9. PMID: 29132759.

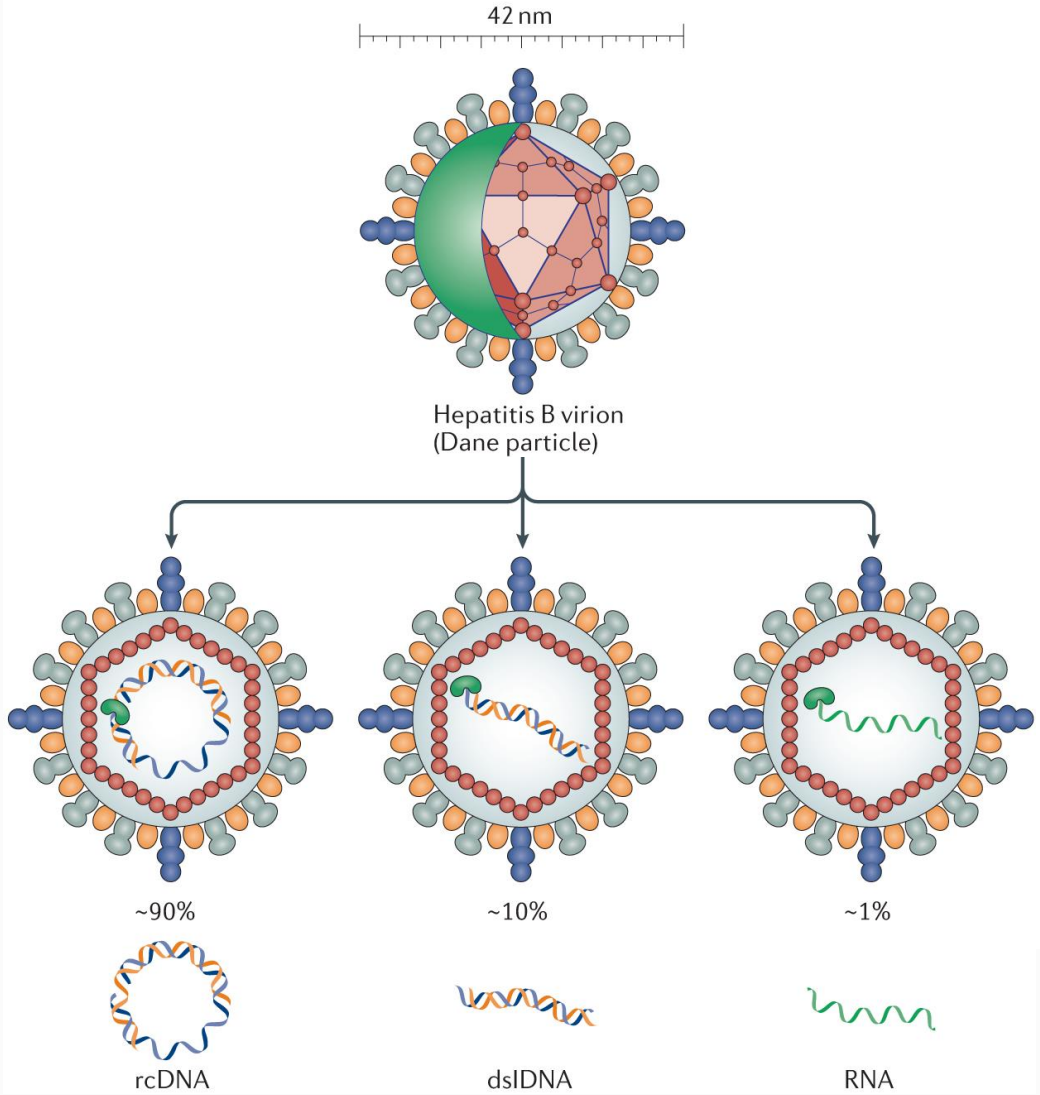
WHO Global Hepatitis strategy

- To eliminate viral hepatitis as a global health threat by 2030

- Requires: 80% of treatment-eligible people to be on treatment for both HBV and HCV







The Dane particle

Human HBV is a member of the *Hepadnaviridae* family

Circulating hepatitis B virions.

Equipped with an envelope accommodating three in-frame viral gene products.

Large envelope Middle envelope Small envelope

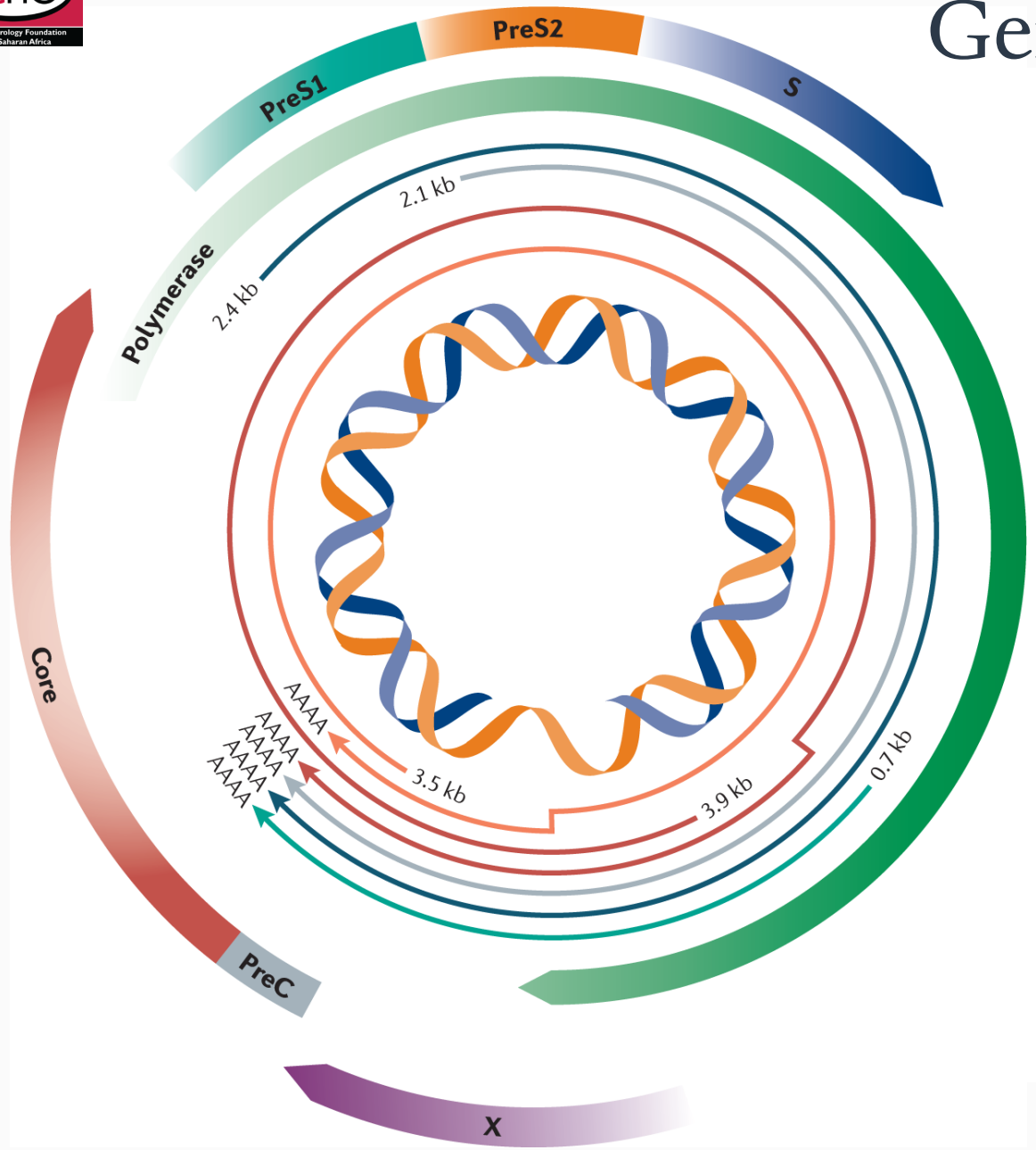
The envelope encloses an inner nucleocapsid particle (~28 nm)

- Contains 120 core protein homodimers assembled into an icosahedral structure.

Nucleocapsid particles contain a copy of a relaxed circular partially double-stranded DNA genome of ~3.2 kb, and a copy of the viral polymerase.

Iannacone M, Guidotti LG. Immunobiology and pathogenesis of hepatitis B virus infection. Nat Rev Immunol. 2022 Jan;22(1):19-32. doi: 10.1038/s41577-021-00549-4. Epub 2021 May 17. PMID: 34002067.

Genomic Structure of HBV



The inner helixes represent the partially double-stranded, relaxed circular hepatitis B virus (HBV) DNA genome.

The outer thin lines represent the six capped, polyadenylated and overlapping RNAs.

3.5-kb RNA represents two transcripts that differ from one another by only a few nucleotides.

- The slightly longer transcript encodes for the precore protein (PreC)
- The slightly shorter one encodes for both the core protein and the polymerase protein.

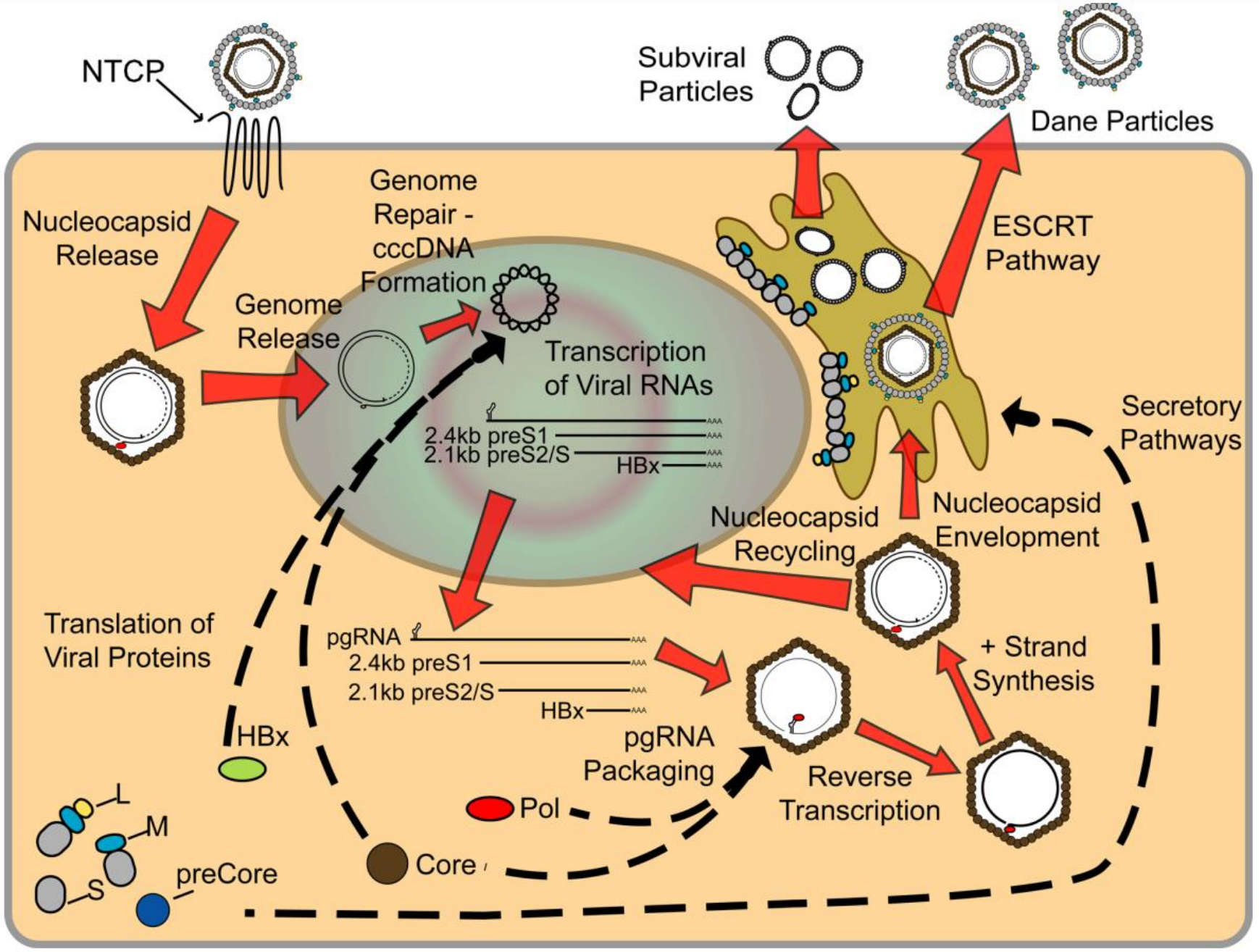
The 3.9-kb RNA is thought to represent a long form of a HBV xRNA; note that the canonical HBV xRNA is 0.7 kb in length.

The 2.4-kb RNA encodes for the PreS1 (or L) envelope protein.

The 2.1-kb RNA encodes →PreS2 and S envelope proteins (also called M and S).

The outermost color lines indicate the translated HBV proteins.

Iannacone M, Guidotti LG. Immunobiology and pathogenesis of hepatitis B virus infection. Nat Rev Immunol. 2022 Jan;22(1):19-32. doi: 10.1038/s41577-021-00549-4. Epub 2021 May 17. PMID: 34002067.



Lamontagne RJ, Bagga S, Bouchard MJ. Hepatitis B virus molecular biology and pathogenesis. Hepatoma Research. 2016; 2:163-86. http://dx.doi.org/10.20517/2394-5079.2016.05

NATURAL HISTORY OF CHRONIC HBV

PHASE 1: HBeAg +ive Chronic HBV Infection

- Previous terminology: Immune Tolerant
- Characterized by:
  - Presence of HBeAg
  - Very high levels of HBV DNA:>200 000 IU/ml
  - ALT persistently normal (ULN or approx. <40)
  - None or minimal necroinflammation or fibrosis
- Phase prolonged in patients infected perinatally & a/w preserved HBV specific T-cell function at least until young adulthood
- Pts are highly contagious (Very high HBV DNA) = integration of HBV DNA & production of Clonal Hepatocytes expansion = hepatocarcinogenesis
- Rate of spontaneous HBeAg loss is very low

PHASE 2: HBeAg +ive Chronic Hepatitis

- Previous Terminology: Immune Reactive HBeAg +ive
- Characterized by:
  - Presence of HBeAg
  - High levels of HBV DNA (but < phase 1): > 20 000 IU/ml
  - Raised ALT
  - Moderate to sever liver necroinflammation → accelerated progression to fibrosis
- May occur several years after phase 1 but rapidly reaches phase 2 if patients were infected during adulthood
- Outcome is variable

Variable outcome

Phase 3

Phase 4

Phase 3: HBeAg negative HBV infection

- Prev known as Inactive carrier
- Characterized by
  - Presence of Anti Hbe
  - HBV DNA – undetectable or low (<2 000 IU/mL)
  - Normal ALT
- Pts are @ very low risk of HCC
- HBsAg loss occurs in 1-3% per year

Phase 4: HBeAg negative CHB

- Characterized by
  - Presence of Anti Hbe
  - Persistent or Fluctuating moderate to high HBV DNA > 2 000 IU/ml
  - Persistent or Fluctuating levels of ALT
  - Liver histology shows necroinflammation and fibrosis
- Most pts have HBV variants in pre-core +/- basal core promoter regions that impair or abolish HBeAg expression

Phase 5: Occult HBV infection

- Characterized by:
  - Serum HBsAg negative, Anti HBc +ve
  - Normal ALT
  - HBV DNA usually detectable but < 200 IU/ml
  - cccNDA can frequently be detected in liver
- HCC risk
  - Low if no CoL prior to HBsAg loss
  - Remains if CoL has already developed prior to HBsAg loss, hence need for HCC surveillance – only if CoL
  - Immunosuppression may lead to HBV reactivation

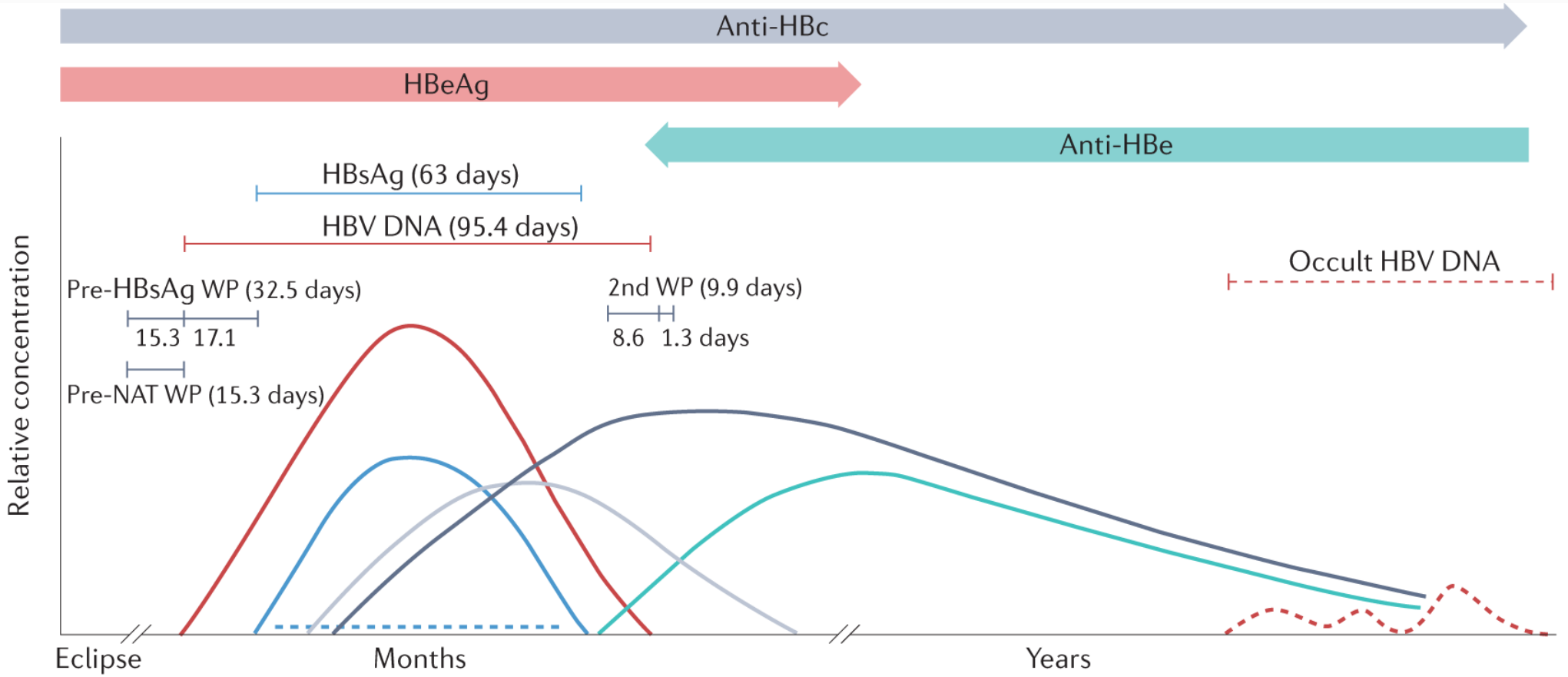
Phases of Chronic HBV

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

Chronic hepatitis B	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Chronic HBV infection	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



Liver activity	Mild or no necro-inflammation	Moderate-to-severe necro-inflammation	Necro-inflammation	Absent
Phase	High replicative/ low inflammatory	Immune clearance	HBeAg-negative chronic hepatitis	Non or low replicative

HBV DNA — HBsAg — Primary occult HBsAg — Total anti-HBc — IgM anti-HBc — Anti-HBs — Occult persisting HBV DNA

Kramvis, A., Chang, KM., Dandri, M. et al. A roadmap for serum biomarkers for hepatitis B virus: current status and future outlook. Nat Rev Gastroenterol Hepatol 19, 727–745 (2022). https://doi.org/10.1038/s41575-022-00649-z

Initial Assessment of the Patient

Complete history

Physical examination:

Assessment of liver disease activity, severity and markers of HBV infection

- Biochemical parameters (AST,ALT, GGT, ALP, Bilirubin, Albumin, FBC, PT)
- HBeAg and anti-HBe detection are essential for the determination of the phase of chronic HBV infection
- HBV DNA serum level → for dx, establishment of phase of infection, decision to treat and subsequent monitoring.
- HBV genotype is not necessary in the initial evaluation
  - Useful for selecting patients to be treated with IFNa offering prognostic information for the probability of response to IFNa therapy and the risk of HCC
- Anti-HAV should be performed, and patients with negative anti-HAV should be advised to be vaccinated against HAV

USS is recommended in all patients.

Extrahepatic manifestations

Acute HBV infection

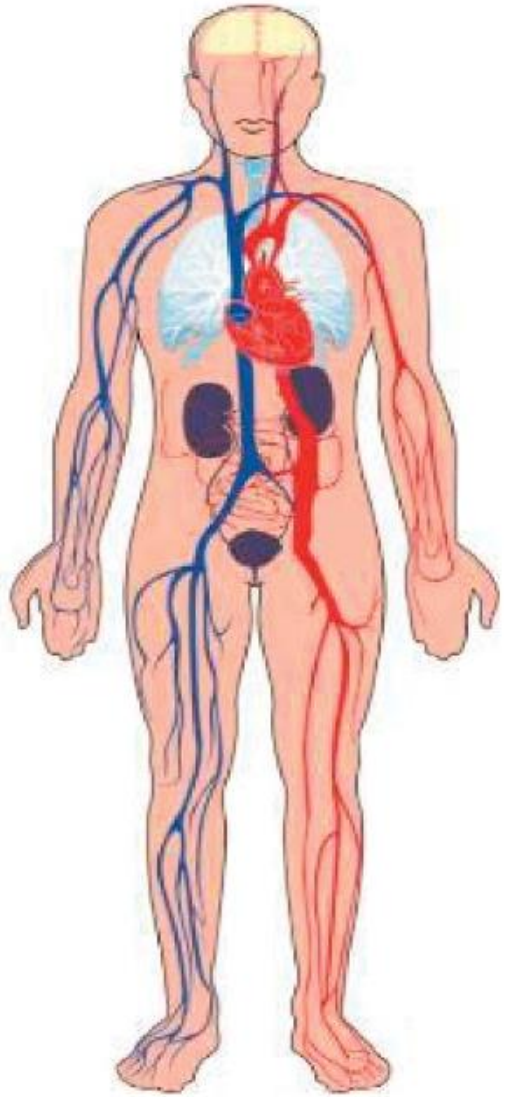
Systemic
- Flu-like syndrome
- Serum sickness
- Polyarteritis nodosa *
- Cryoglobulinemia *

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

Liver Bx & Non-invasive tests (NITs)→ to determine disease activity in cases where biochemical and HBV markers reveal inconclusive results.

NITs: APRI, FIB-4 scores and FibroTest (commercially available blood markers).

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

Transient elastography (Fibroscan) offers the highest diagnostic accuracy for the detection of cirrhosis vs other NTIs.

APRI score > 2 or liver stiffness mean cut-off of 12.5 kPa (on FibroScan) = cirrhosis.

APRI score > 1.5 or liver stiffness of > 7 kPa (on FibroScan) = significant fibrosis.

Severe fibrosis or CoL is when:

- **Normal ALT with Liver stiffness > 9kPa or**
- **Raised ALT but <5x UNL with Liver stiffness > 12 kPa**

All first degree relatives and sexual partners to be tested for HBV serological markers (HBsAg, anti-HBs, anti-HBc)
to vaccinated if they are negative

R/O Alcoholic, autoimmune, metabolic liver disease with steatosis or steatohepatitis and other causes of chronic liver disease should be systematically excluded including co-infections with hepatitis D virus (HDV), hepatitis C virus (HCV) and HIV.

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
- Present in HBeAg –ve CHB with active replication due to mutant strains

Anti-HBc total (HBcAb total) = IgM +IgG
- *IgM anti HBc* – acute infection or reactivation or Flare
- *IgG anti HBc* – Most sensitive marker of past infection. (note: HBsAb may be undetectable if infection acquired in childhood)

Interpretation of screening tests for HBV infection

Screening Test Results					
HBsAg	Anti-HBc	Anti-HBs	Interpretation	Management	Vaccinate?
+	+	–	Chronic hepatitis B	Additional testing and management needed	No
–	+	+	Past HBV infection, resolved	No further management unless immunocompromised or undergoing chemotherapy or immunosuppressive therapy	No
–	+	–	Past HBV infection, resolved or false-positive	HBV DNA testing if immunocompromised patient	Yes, if not from area of intermediate or high endemicity
–	–	+	Immune	No further testing	No
–	–	–	Uninfected and not immune	No further testing	Yes

Terrault, Norah A.,1; Lok, Anna S.F.2; McMahon, Brian J.3; Chang, Kyong-Mi4; Hwang, Jessica P.5; Jonas, Maureen M.6; Brown, Robert S. Jr.7; Bzowej, Natalie H.8; Wong, John B.9. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67(4):p 1560-1599, March 25, 2018. | DOI: 10.1002/hep.v67.4*

TREATMENT

Main goals of therapy:

- To **improve survival** and **QoL** by **preventing** disease **progression,** and consequently **HCC** development.

Additional goals:

- Prevent mother to child transmission
- Prevent hepatitis B reactivation
- Prevention & Rx of HBV-associated extrahepatic manifestations.
- Regression of fibrosis and cirrhosis in patients with established advanced fibrosis or cirrhosis
- In pts with HCC, to suppress viral HBV replication & reduce HCC recurrence after potential curative therapy
- In Acute Hepatitis, to prevent ALF, improve QoL by shortening the duration of symptoms and lower risk of chronicity

End points of therapy

The **induction of long-term suppression** of **HBV DNA levels** represents the main endpoint of all current treatment strategies (Evidence level I, grade of recommendation 1).

The **induction of HBeAg loss**, with or without anti-HBe seroconversion, in HBeAg-positive CHB patients is a valuable endpoint, as it often represents a partial immune control of the chronic HBV infection (Evidence level II-1, grade of recommendation 1).

A **biochemical response defined as ALT normalisation** should be considered as an additional endpoint, which is achieved in most patients with long-term suppression of HBV replication (Evidence level II-1, grade of recommendation 1).

HBsAg loss, with or without anti-HBs seroconversion, **is an optimal endpoint**, as it indicates profound suppression of HBV replication and viral protein expression (Evidence level II-1, grade of recommendation 1).

Indication of Rx

- All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated (Evidence level I, grade of recommendation 1).
- Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (Evidence level I, grade of recommendation 1).
- Patients with HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of the degree of fibrosis (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions (Evidence level III, grade of recommendation 2).
- Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled (Evidence level III, grade of recommendation 2).

EASL

Cirrhosis of liver

HCC

Family History of HCC or ? CoL

Extrahepatic Manifestation

If no CoL:

- HBV DNA >2000 with Raised ALT with moderate necroinflammation = start treat
- Even if ALT is normal but DNA >2000 with moderate necroinflammation = start treatment
- HBV DNA > 20,000 with ALT > 2x UNL = start treatment irrespective of degree of necroinflammation
- HBeAg +ve Chronic HBV infection + Patient > 30years, regardless of liver fibrosis → may be treated

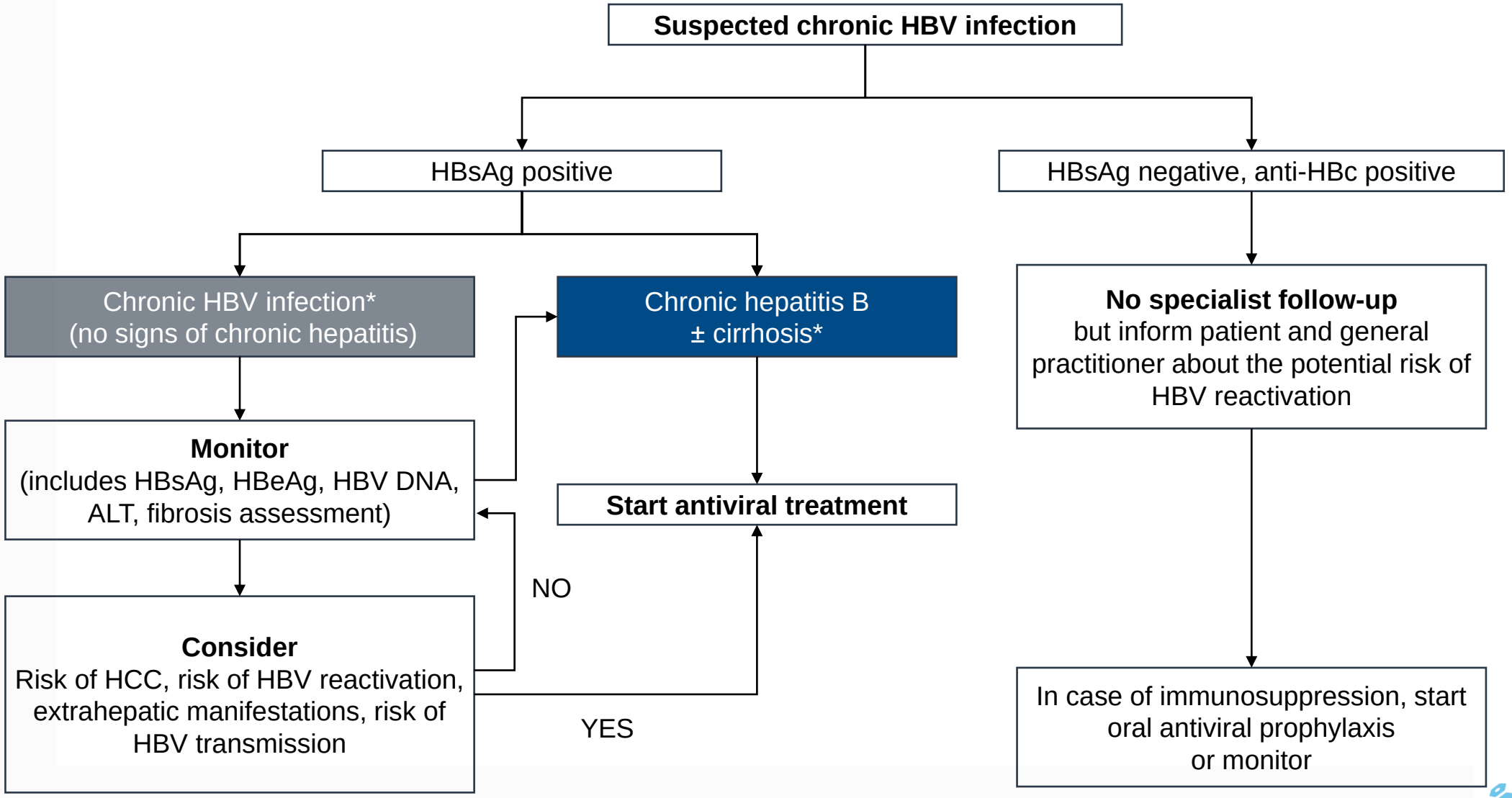
Monitoring patients currently not on Rx

Monitoring parameters = ALT + DNA level + NITs
No indication for treatment
Normal ALT levels

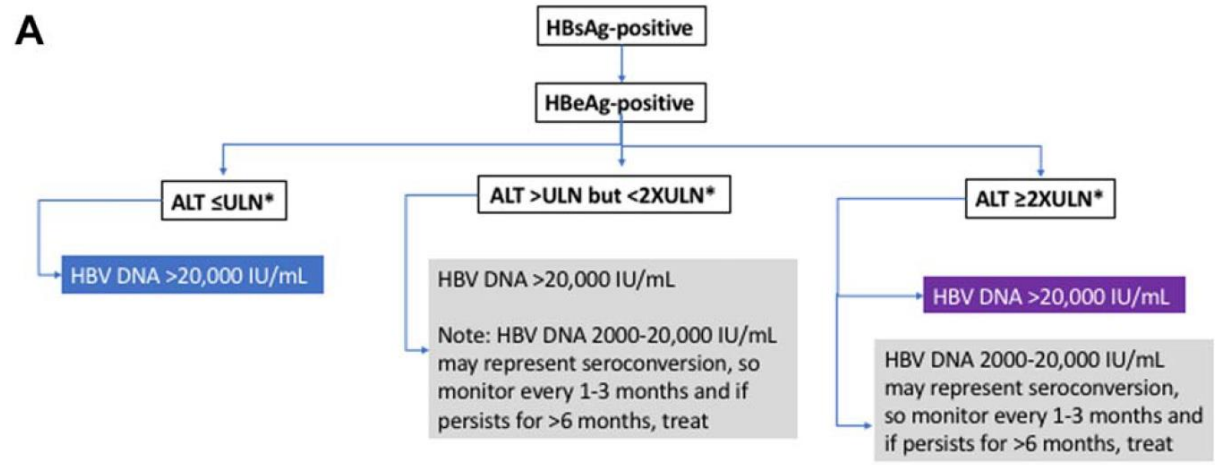
F/u intervals:

- 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 3monthly x 1year then 6 monthly

Algorithm for the management of HBV infection



Patients without Cirrhosis

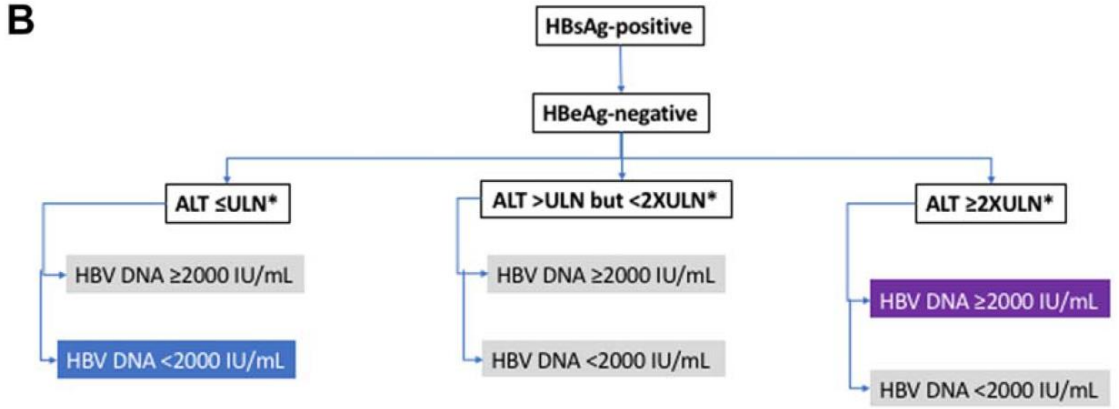


Recommendations:

Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBeAg every 6-12 months.

Exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If other causes of ALT >ULN excluded and elevation persists, treat, especially if age >40.



Recommendations:

Treat

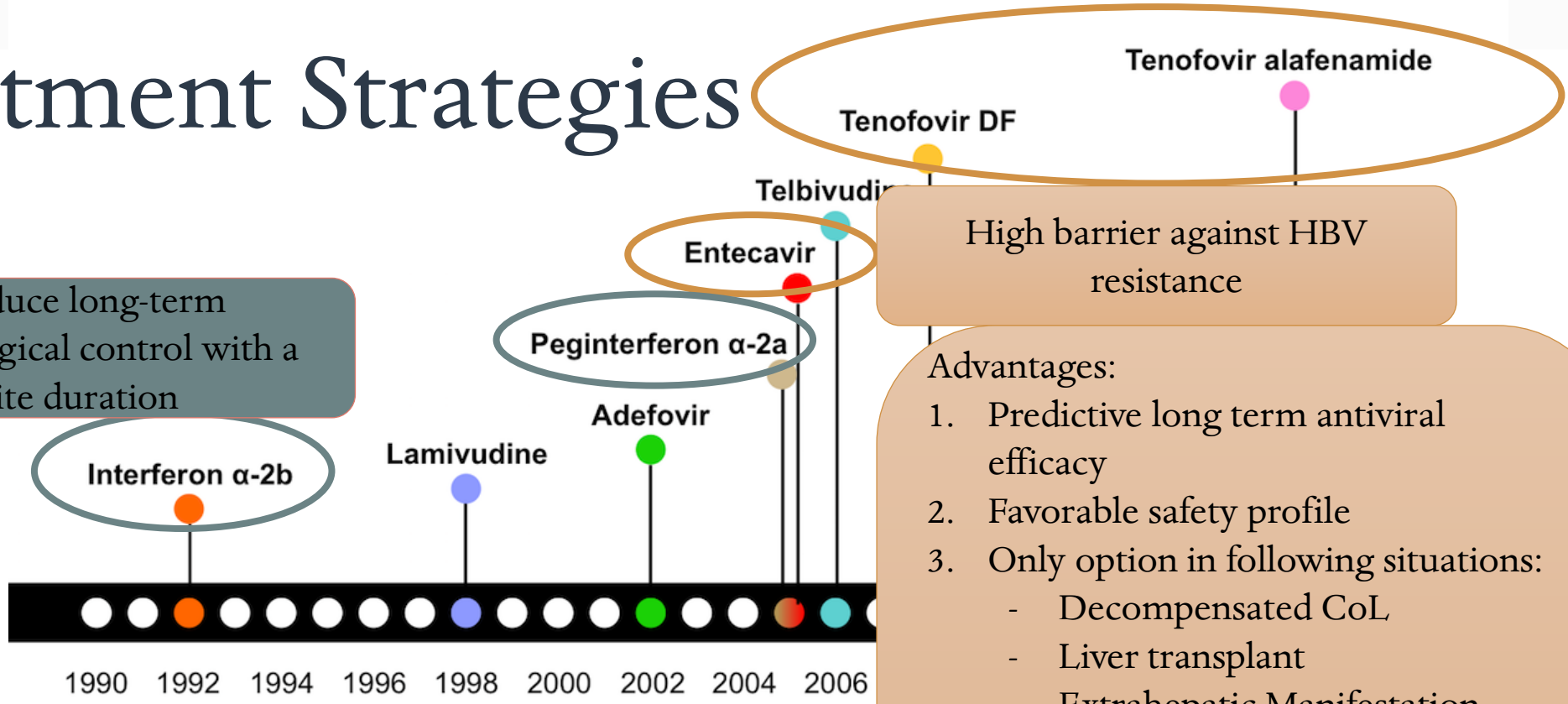
Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg annually.

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.
If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT >ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.

***The upper limits of normal for ALT in healthy adults are reported to be 29-33 U/L for males and 19-25 U/L for females. An upper limit of normal for ALT of 35 U/L for males and 25 U/L for females is recommended to guide management decisions.**

Terrault, Norah A.,1; Lok, Anna S.F.2; McMahon, Brian J.3; Chang, Kyong-Mi4; Hwang, Jessica P.5; Jonas, Maureen M.6; Brown, Robert S. Jr.7; Bzowej, Natalie H.8; Wong, John B.9. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67(4):p 1560-1599, March 25, 2018. | DOI: 10.1002/hep.v67.4*

Treatment Strategies



To induce long-term immunological control with a finite duration

High barrier against HBV resistance

Advantages:

1. Predictive long term antiviral efficacy
2. Favorable safety profile
3. Only option in following situations:
   - Decompensated CoL
   - Liver transplant
   - Extrahepatic Manifestation
   - Acute hepatitis B
   - Severe Chronic HBV exacerbations
   - HBV prevention for immunosuppression

Disadvantages:

1. Highly variable response to treatment
2. Unfavorable safety profile
   (Flu like ill ness, thyroid dysfunction, Fatigue, Myelosupression)

TDF vs TAF

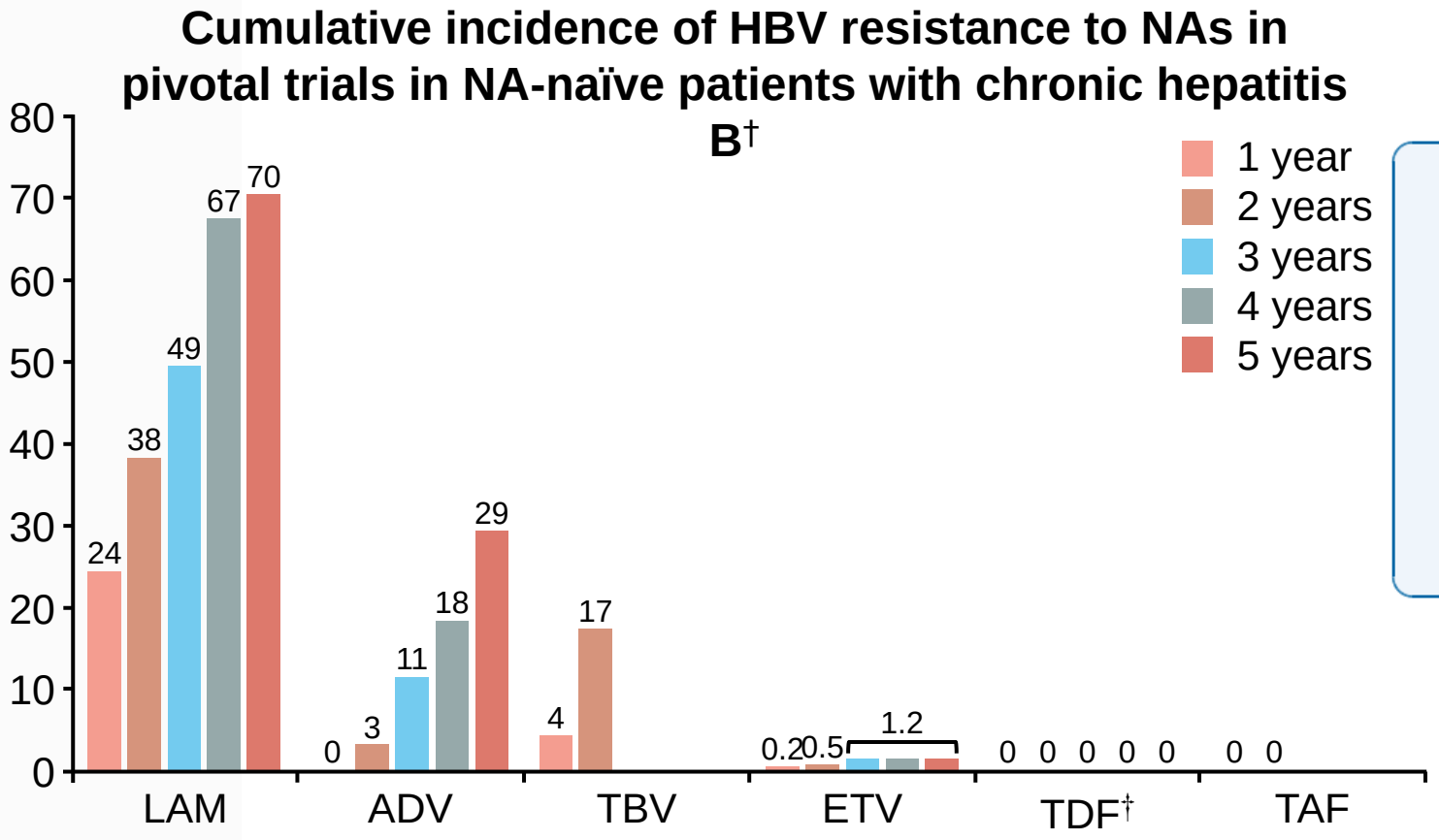
TDF	TAF
25% oral bioavailability	40% oral bioavailability
300mg (needs high dose to concentrate in hepatocytes, WBC)	25mg – 90% lower serum circulating levels, but non-inferior efficacy
Decreased bone mineral density	-
Renal toxicity	-
Distributed to a wide range of tissues	Selective to WBC and hepatocytes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

Selecting ETV / TAF over TDF

Age	• >60 years
Bone disease	• Chronic steroid use or use of other medications that worsen bone density • History of fragility fracture • Osteoporosis
Renal alteration†	• eGFR <60 ml/min/1.73 m^2 • Albuminuria >30 mg/24 h or moderate dipstick proteinuria • Low phosphate (<2.5 mg/dl) • Haemodialysis

Prevention of resistance should rely on the use of first-line NAs with a high barrier to resistance



- The long-term administration of a potent NA with high barrier to resistance is the treatment of choice regardless of the severity of liver disease (Evidence level I, grade of recommendation 1).
- The preferred regimens are ETV, TDF and TAF as monotherapies (Evidence level I, grade of recommendation 1).
- LAM, ADV and TBV are not recommended in the treatment of CHB (Evidence level I, grade of recommendation 1).

Definition 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	

Managing NA Failure

Treatment should be adapted as soon as virological failure under NAs is confirmed*

Resistance pattern	Recommended rescue strategies
LAM resistance	Switch to TDF or TAF
TBV resistance	Switch to TDF or TAF
ETV resistance	Switch to TDF or TAF
ADV resistance	If LAM-naïve: switch to ETV or TDF or TAF If LAM-resistant: switch to TDF or TAF If HBV DNA plateaus: add ETV† or switch to ETV
TDF or TAF resistance‡	If LAM-naïve: switch to ETV If LAM-resistant: add ETV§
Multidrug resistance	Switch to ETV + TDF or TAF combination

Stopping NAs

Long-term therapy with NAs is usually required

HBV eradication is not usually achieved

- NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion (Evidence level II-2, grade of recommendation 1).
- NAs can be discontinued in non-cirrhotic HBeAg-positive CHB patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted (Evidence level II-2, grade of recommendation 2).
- Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term ($\geqslant$3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed (Evidence level II-2, grade of recommendation 2).

Special Considerations in HBV

HBV & Decompensated Cirrhosis

Goal: Complete viral suppression in the shortest time possible. to achieve clinical recompensation and to avoid liver transplantation

Treated with NAs as early as possible. ETV or TDF (preferred drugs)

Dose of ETV = 1 mg (instead of 0.5 mg in compensated disease) OD

Studies concerning the safety and efficacy of TAF in these patient populations are lacking.

PegIFNa is contraindicated

Referred for liver transplantation

Lifelong treatment is recommended

The risk of developing HCC is high

HIV-HBV co-infection

Recommended to initiate ART in HIV/HBV coinfected patients irrespective of CD4 cell count d/t the increased risk of fibrosis progression, cirrhosis and HCC

ART should include either TDF or TAF

Avoid stopping TDF- or TAF-containing ART → d/t high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis

Monitor Renal functions, liver functions and Bone mineral density closely

HIV-HBV mortality 2x greater than HIV-HCV mortality

CD4 count <200 cells/mL 16 times greater than CD4 count >350cells/mL

Increased risk of perinatal HBV infection

HCV-HBV coinfection

Accelerates progression of liver disease and HCC

HCV usually greater contributor to liver disease

SVR rates 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 – consider prophylaxis until 12 weeks post DAA therapy
- Occult hepatitis B – Monitor closely and investigate for reactivation of rising ALT

PMTCT

Vertical transmission is common

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

Currently no formal program for HBsAg screening in pregnancy

WHO recommends screening if prevalence >2%

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.

PMTCT

HBV screening should be done in 1st trimester

Those not vaccinated should be vaccinated

If HBsAg positive

- Referred for further testing, counselling and medical management
- Contact tracing to identify others that are infected
- If immune tolerant or immune control phase: do not require treatment – BUT need to consider risk of transmission with HBV VL >200 000 IU/mL
- HBIG + birth dose vaccine within 24 hours of delivery prevent 85-90% of MTCT
- Consideration of TDF 300mg for all pregnant CHB in 3rd trimester and 12 weeks post partum – to consider criteria for treatment thereafter

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.

Patients undergoing Immunosuppressive therapy

The risk of HBV reactivation high (>10%), moderate (1–10%) or low (<1%).

All patients should be screened with HBsAg, anti-HBs and anti-HBc prior to immunosuppression treatment.

Vaccination of HBV seronegative patients is recommended.

Higher doses or reinforced vaccine may be required to achieve anti-HBs response in immunocompromised patients.

All these patients should start potent NA as a treatment or as prophylaxis.

HBsAg positive patients

- Patients with chronic hepatits B should be treated with ETV, TDF or TAF, similarly to the immunocompetent patients.
- Monitoring and stopping rules for NAs are the same with the immunocompetent patients.
- Prophylactic LAM → reduces risk of HBV reactivation & morbidity and mortality.
- ETV, TDF, TAF is recommended for prophylaxis.
- Continue prophylaxis for at least 12 months (18 months for rituximab-based regimens) after cessation of the immunosuppressive treatment
- Discontinue prophylaxis only if the underlying disease is under remission.
- LFT + HBV DNA every 3 to 6 months during prophylaxis and for at least 12 months after NA withdrawal as a large proportion of HBV reactivations develops after NA discontinuation.

HBsAg-negative, anti-HBc positive patients

- Tested for serum HBV DNA before immunosuppression.
- If viremic, they should be treated similarly to HBsAg-positive patients.
- In high risk group(>10% chance of reactivation), including anti-HBc positive pts needing rituximab or undergoing stem cell transplantation, antiviral prophylaxis is recommended.
  - Prophylaxis should continue for at least 18 months after stopping immunosuppression
  - Monitor for at least 12 months after prophylaxis withdrawal.
  - LAM may be used safely (but few cases of HBV exacerbation due to LAM resistance reported)
  - Prophylaxis with ETV or TDF or TAF can be also considered
- In moderate (<10%) or low (<1%) risk of HBV reactivation, pre-emptive therapy, not prophylaxis, is generally recommended.
  - The main virological events are HBsAg reappearance (seroreversion) or detection of HBV DNA = hepatitis flare (life threatening)
  - Monitoring HBsAg +/- HBV DNA every 1– 3 months during and after immunosuppression,
  - ETV, TDF or TAF treatment in such cases
  - NA should be started as early as possible, independently of ALT levels.

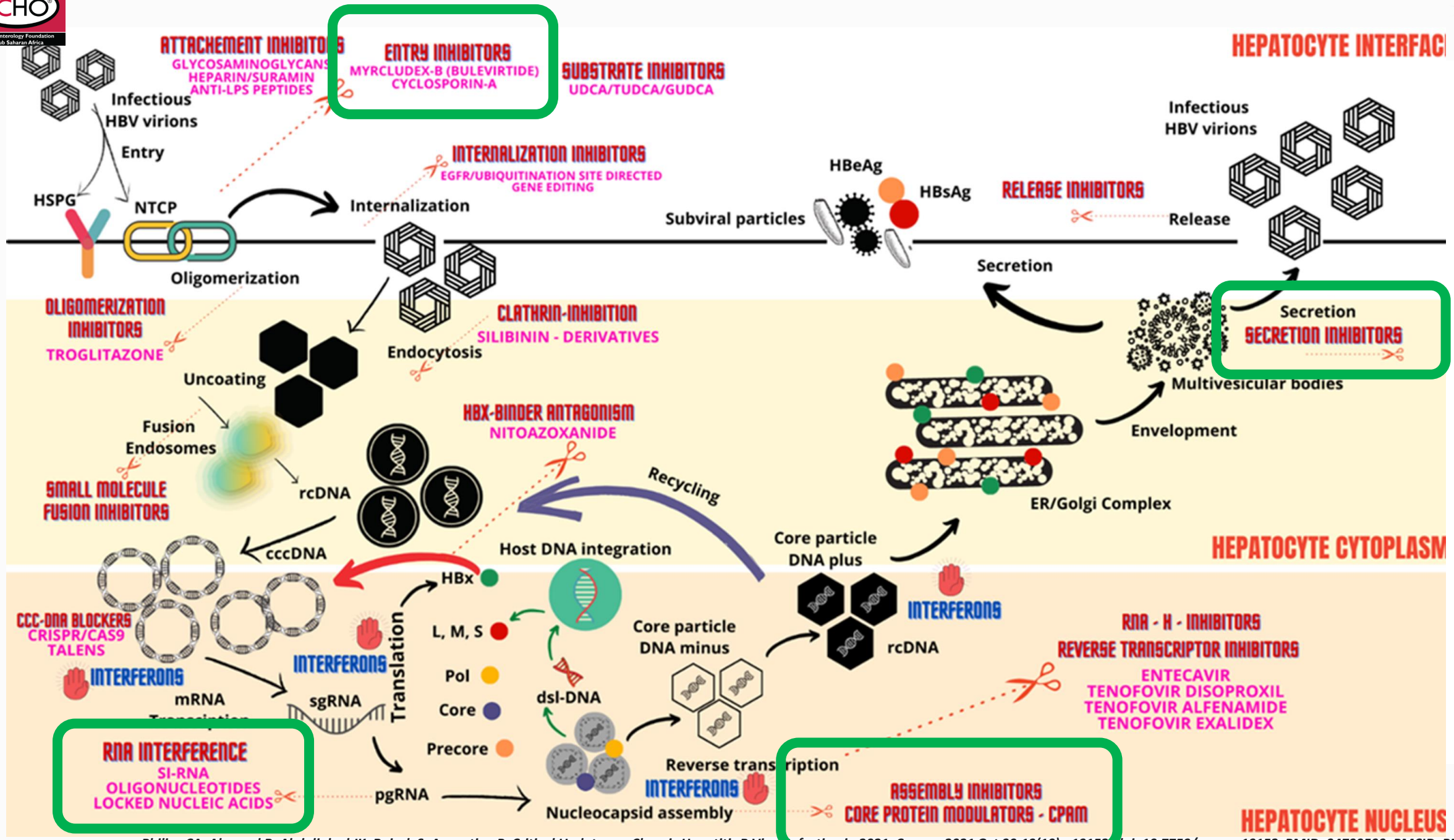
Extrahepatic Manifestations

- Patients with replicative HBV infection and extrahepatic manifestations should receive antiviral treatment with NA (Evidence level II-2, grade of recommendation 1).
- PegIFNα should not be administered in patients with immune-related extrahepatic manifestations (Evidence level III, grade of recommendation 1).

Responds well to antiviral therapy.

PegIFNa can worsen some immune mediated extrahepatic manifestations, hence should be avoided in immune-related extrahepatic manifestations.

Plasmapheresis, corticosteroids and potentially other immune-suppressive drugs during the initial phase can be useful in addition to NA therapy in special cases.



Philips CA, Ahamed R, Abduljaleel JK, Rajesh S, Augustine P. Critical Updates on Chronic Hepatitis B Virus [illegible]fection in 2021. Cureus. 2021 Oct 20;13(10):e19152. doi: 10.7759/cureus.19152. PMID: 34733599; PMCID: PMC8557099.

Thank You


HEPATITIS B
VACCINE
HbV
(Recombinant)
Pediatric/Adolesce
10 ml/10 doses