Hepatitis B: Update 2022 and beyond

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Disclosures

- See robertgish.com

- Resources are also at robertgish.com for HBV and all forms of liver disease and liver health

- Please subscribe to my newsletter via my website

- If you send me an Email, I can place you on an internal HBV listserv as well, for additional educational material

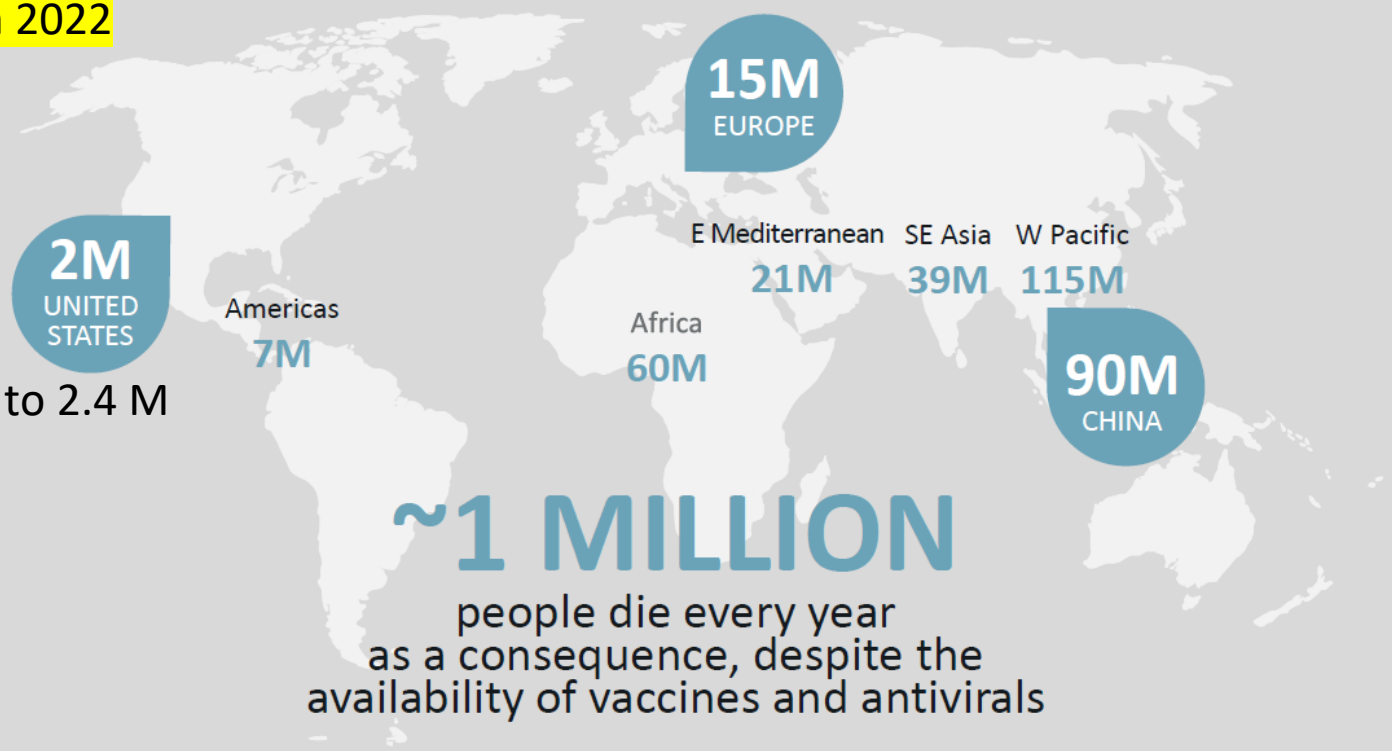
Objectives

- Describe he epidemiology and virology of hepatitis B and how this links to testing and linkage to care
- Summarize the natural history of hepatitis B
- Recommend screening for HBV: Test all adults with triple panel
- Facts and Fictions of HBV:
  - HBV is blood transmitted
  - Clarity of anti-HBc test interpretation and linkage to care
- Treatment options for HBV: Consider to treat all HBV DNA+
- Pregnancy
- Liver Transplant
- New Treatments
- Vaccination: Current discussions
- 5 line guidelines

Tremendous Medical Need

257 million people are chronically infected with HBV globally

272 million in 2022



US data is up to 2.4 M

Hepatitis B. WHO (2017). http://www.who.int/mediacentre/factsheets/fs204/en/.

HBV Disease Progression

~ 2 people per minute will die from complications associated with HBV

Chronic Infection

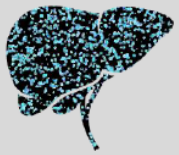
>250 million chronically infected worldwide

8% diagnosed

<1% receive treatment

1%-3% of those receiving treatment with current options achieve functional cure

Cirrhosis/HCC



20%-30%

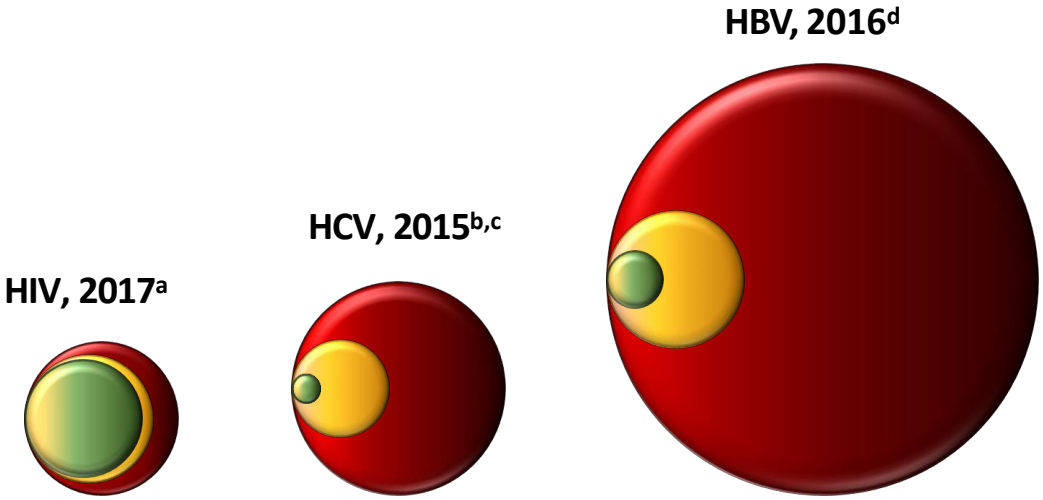
Surgery, chemotherapy, and liver transplant

Death

~1 million people/year

2 people/minute

Gaps – HIV, HCV, HBV



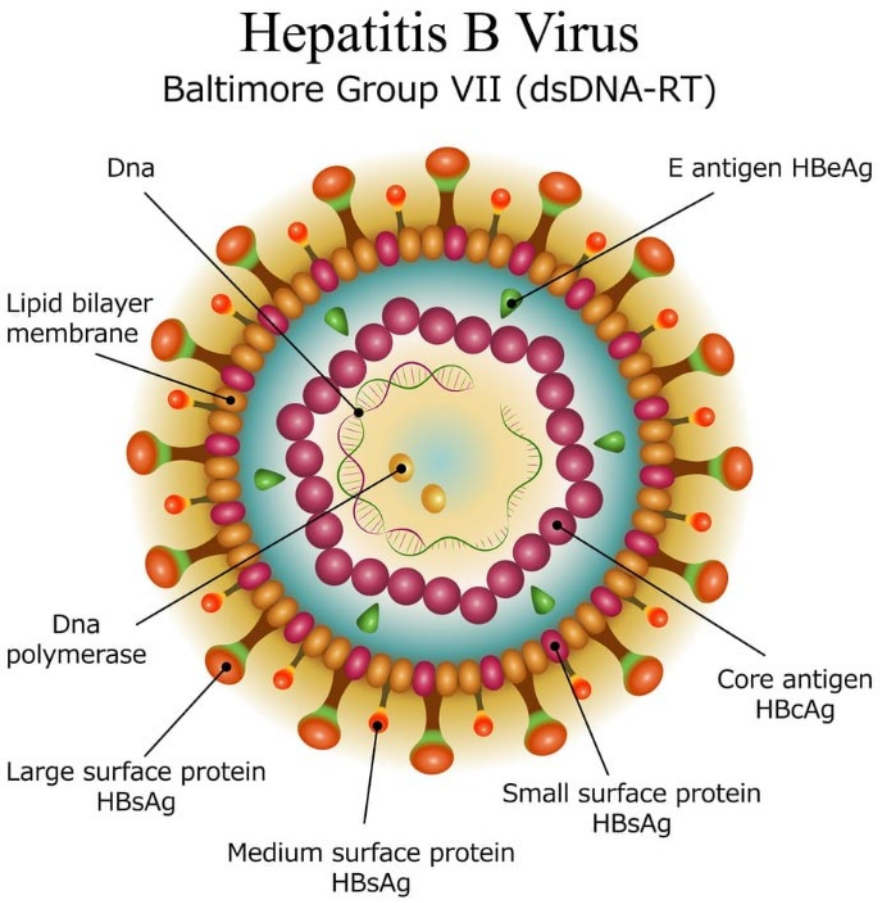
Global estimates of patients (millions)

Prevalence	36.9	71.1	292.0
Diagnosed	27.7	14.2	28.8
Treated	21.7	1.1	4.8

a. UNAIDS Fact Sheet 2018. Available at: http://www.unaids.org/en/resources/fact-sheet (accessed April 2019);
b. Blach S, et al., Lancet Gastroenterol Hepatol, 2017:2;161–76.
c. WHO Global Hepatitis Report, 2017. Available at: http://www.who.int/hepatitis/publications/global-hepatitis-report2017-executive-summary/en/ (accessed April 2019);
d. Razavi-Shearer D, et al. Lancet Gastroenterol Hepatol 2018:3;383–403;

Acknowledgment: John Martin

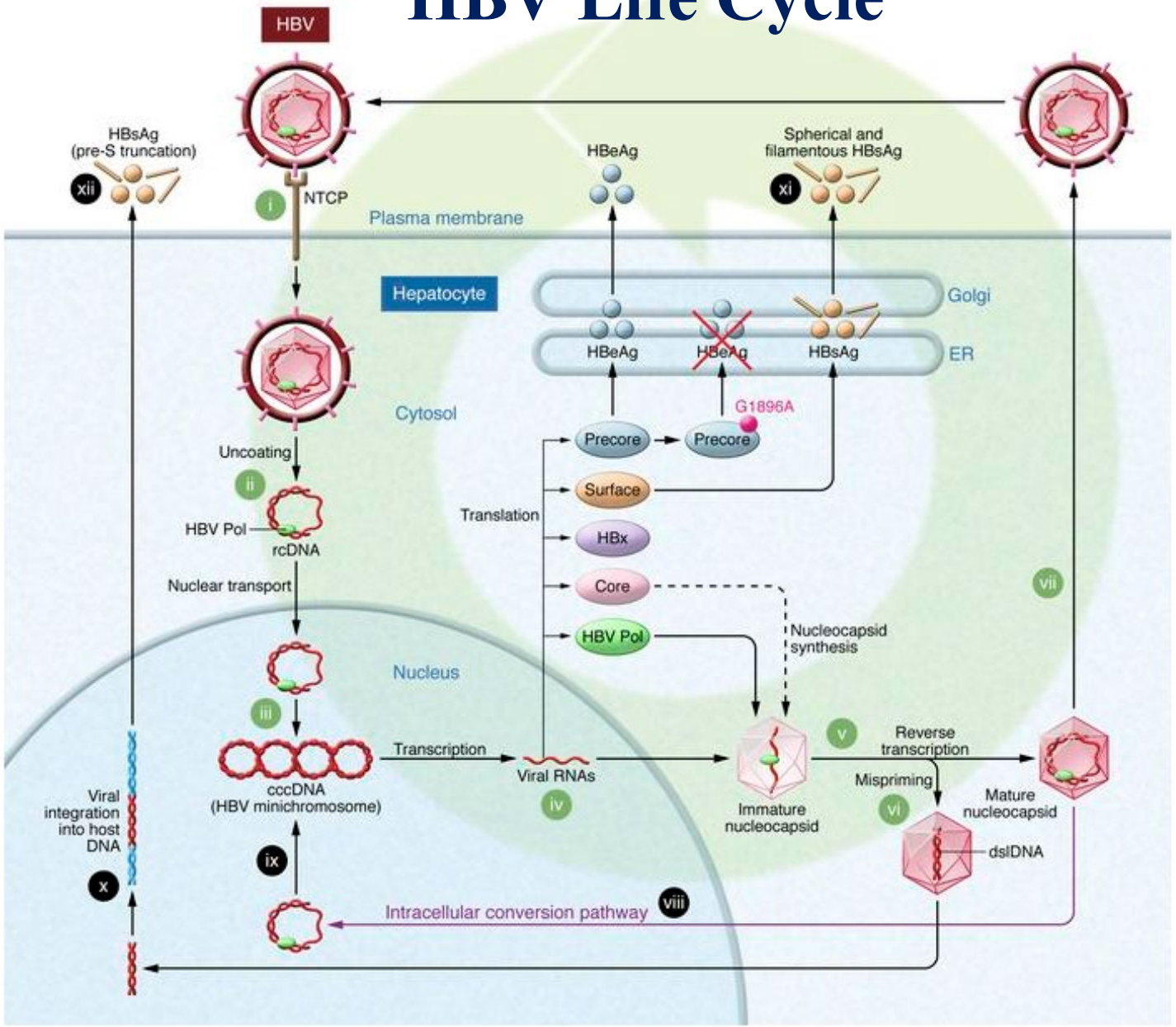
Hepatitis B Virus ("Hepadnavirus")



- DNA virus
- Other hosts for hepadnaviruses include woodchucks, Peking ducks, ground squirrels, herons, and more
- HBV replicates through an RNA intermediate and can integrate into the host genome
- 10 HBV genotypes, A- J
- cccDNA

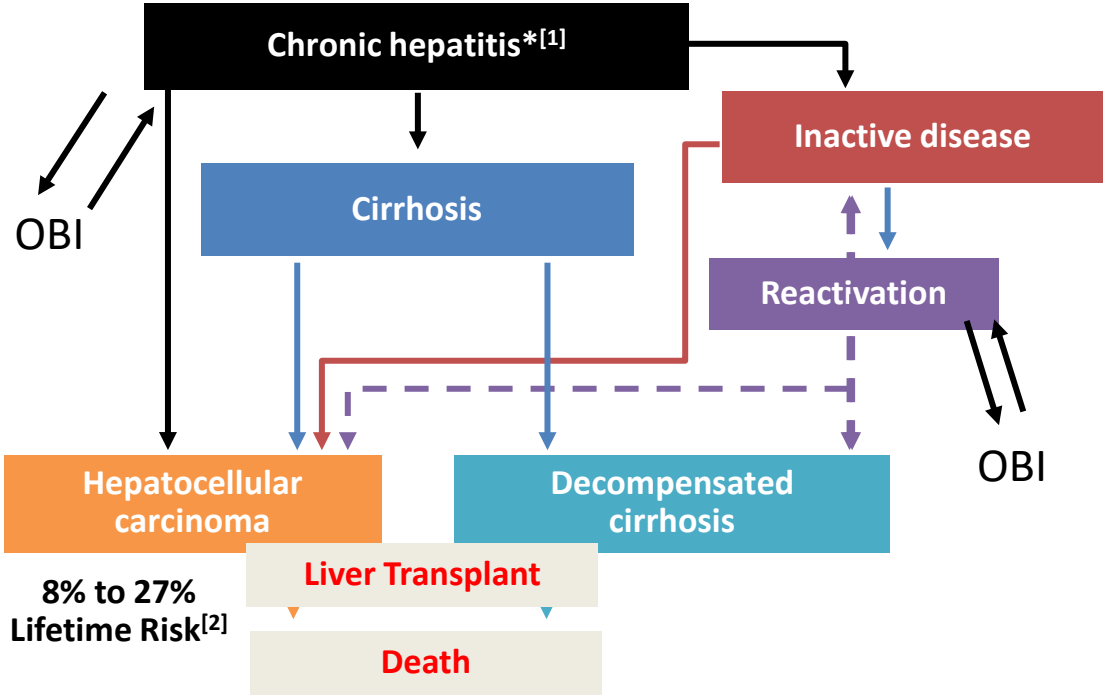
Courtesy of: Oligonucleotide Therapeutics Society

HBV Life Cycle



Revill PA, Locarnini SA J Clin Invest 2016:126:833-836

Hepatitis B Disease Progression and Impact



*Failure to clear HBsAg 6 mos after acute infection.

Up to 40% of persons with CHB develop significant clinical consequences, including cirrhosis, liver failure, and HCC[3]

25% of persons with CHB will die prematurely from complications[4]

1. The elimination of hepatitis B. In: Buckley. Eliminating the public health problem of hepatitis B and C in the United States: Phase One Report. 2016.

2. Huang. JCO. 2011;29:3643.

3. Lok. NEJM. 2002;346:1682.

4. Harris. MMWR. 2018;67:541.

HBV Tests Part I:

All patients need this "triple panel" when evaluating for HBV

- +HBsAg = infection (Test all patients for HDV with antibody and qHBsAg)

- +Anti-HBc = exposure = cccDNA = persistence
  - Evaluate for Occult HBV (OBI) if HBsAg (-)
  - Educate about reactivation risk
  - No HBV vaccine boosting recommended

- +Anti-HBs = vaccine immunity, if anti-HBc is negative (if anti-HBc+ "immune control")

- Note:
  - HBV is incurable (see definition of "functional cure")
  - There is no Healthy form/phase of HBV infection
  - There is no "natural immunity"

HBV Tests Part II:
for patients who are HBsAg+

All HBsAg + patients need these tests:

- HBeAg
- Anti-HBe
- HBV DNA quant
- Quant/HBsAg
- HCV antibody
- HAV antibody total
- HIV antibody
- HDV antibody-Total (IgG (not IgM) (IF total +)>> qHDV RNA reflex
- CMP, Liver panel with liver enzymes and liver function, CBC including platelets
- AFP/DCP AFP-L3% and calc GALAD score, Helio, Exact Sciences
- NASH assessment by imaging
- US doppler with spleen and PV size
- Elastography with CAP
- APRI/FIB4

Evaluating the HBsAg + Patient Part III

- ALT/AST : calc ratio
- Family History of HCC and/or cirrhosis
- Alcohol history and current use, PETH testing
- Renal function
- Bone DEXA, Vit D3
- Pregnancy testing if appropriate
- Family testing for HBsAg, anti-HBs, and anti-HBc
- Liver biopsy only if mixed picture of other diseases such as MAFLD, NASH or AIH
  - Consider bx if other noninvasive tests are inconclusive
- Advanced Serum maker panels of fibrosis and inflammation, LiverFast, ELF, Fibrosure/Test

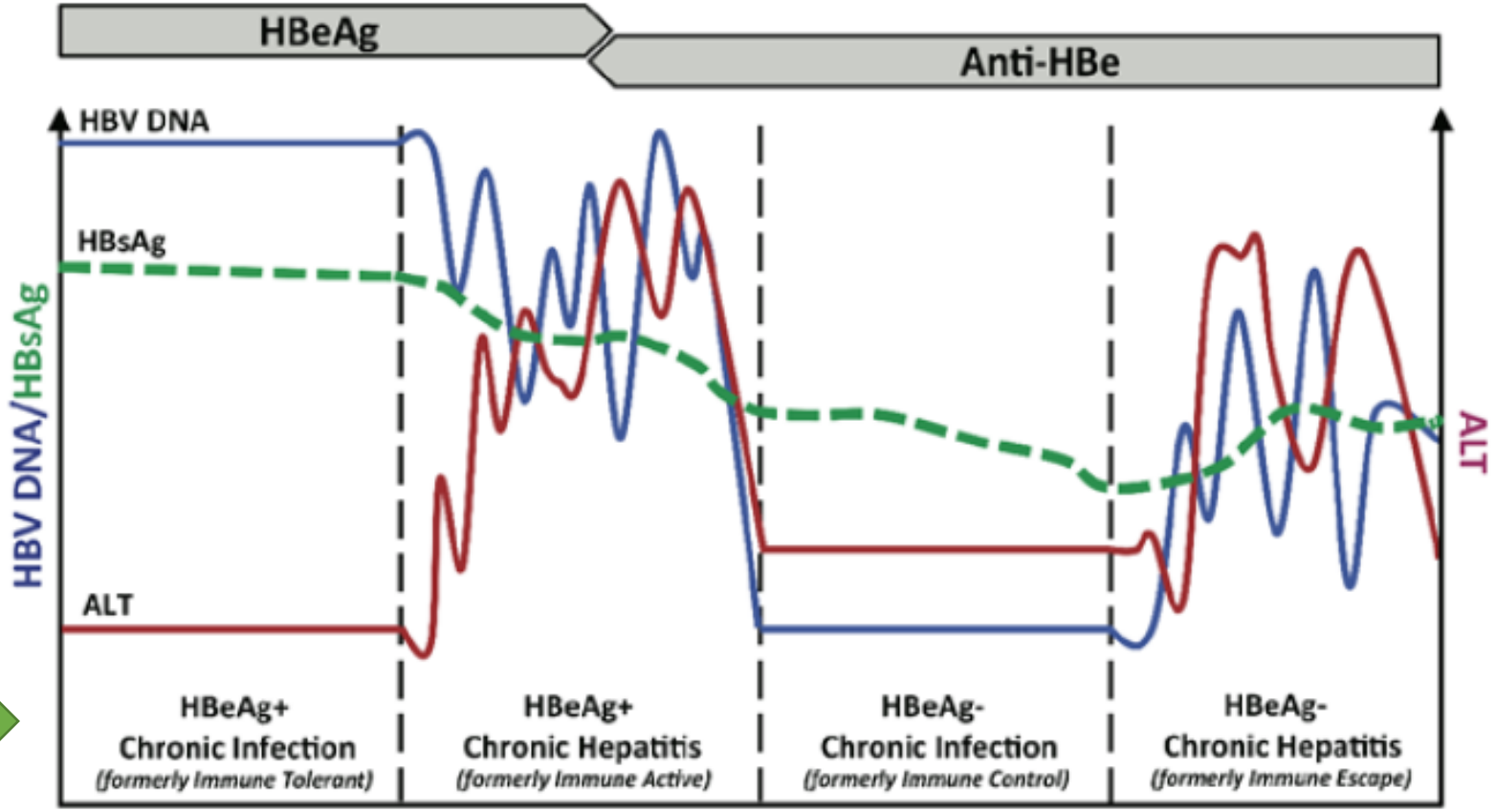
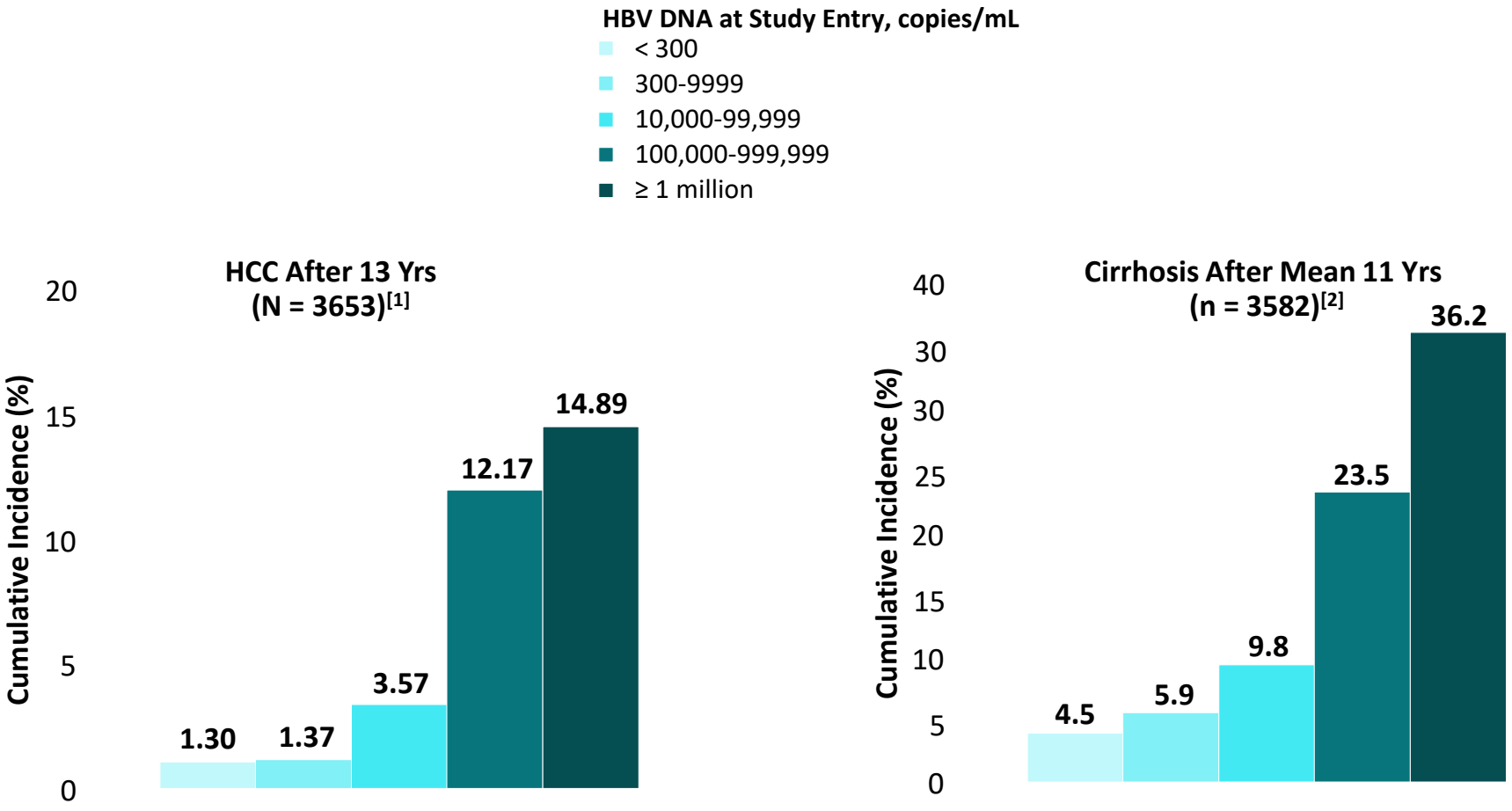


Fig. 1. Disease phases of chronic hepatitis B infection reflecting the updated nomenclature. Representation of the changes/fluctuations in serum HBV DNA (solid blue line) and ALT (solid red line) over the typical course of chronic infection in each disease phase. Proposed levels of HBsAg are shown (dashed green line) as predicted throughout each disease phase.

A focus here on the OLD NAMES

REVEAL-HBV: HBV DNA Levels and Long-term Outcomes



1. Chen. JAMA. 2006;295:65.
2. 2. Iloeje. Gastroenterology. 2006;130:678.

Multivariate-adjusted hazard ratios of developing liver cirrhosis for serum HBV DNA levels at study entry

HBV DNA (copies/mL)	Multivariate-adjusted hazard ratio[a] (95% confidence interval)					
	Cirrhosis (diagnosed with R1 abdominal ultrasonographic test)			Sensitivity analysis removing 100 participants who had only one ultrasound documenting cirrhosis		
	All subjects (n = 3582)	HBeAg-negative subjects (n = 3037)	HBeAg-negative subjects with normal ALT levels (n = 2923)	All subjects (n = 3482)	HBeAg-negative subjects (n = 2960)	HBeAg-negative subjects with normal ALT levels (n = 2850)
<300 (undetectable)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
300-9999	1.4 (0.9-2.2)	1.4 (0.9-2.1)	1.4 (0.9-2.1)	2.0 (1.1-3.6)[b]	1.9 (1.0-3.5)[b]	2.1 (1.1-4.0)[b]
10,000-99,999	2.5 (1.6-3.8)[c]	2.4 (1.5-3.7)[c]	2.5 (1.6-3.9[c]	3.6 (2.0-6.6)[c]	3.4 (1.8-6.2)[c]	3.7 (2.0-7.1)[c]
10,0000-99,9999	5.6 (3.7-8.5)[c]	5.4 (3.5-8.3)[c]	5.6 (3.6-8.7[c]	9.7 (5.4-17.3)[c]	9.1 (5.0-16.4)[c]	10.4 (5.6-19.6)[c]
≥1 million	6.5 (4.1-10.2)[c]	6.7 (4.1-11.0)[c]	6.6 (3.9-11.2)[c]	10.6 (5.7-19.6)[c]	11.6 (6.1-22.1)[c]	12.3 (6.1-25.1)[c]

[a] Trend test, all P<.001
[b] P<.05.[c] P<.001

Chen CJ, et al. Clin Liver Dis 2007; 797-816.

Iloeje UH, et al. . Gastroenterology 2006;130:378–686

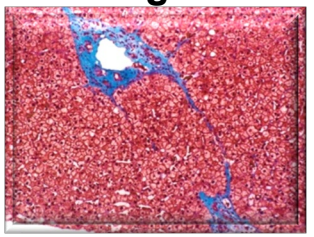
Stage all HBV patients with NonInvastive Testing Progression of Fibrosis in Viral Hepatitis on Biopsy (Metavir)

No Fibrosis

Stage 1

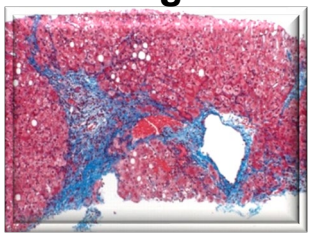
Fibrous expansion of some portal areas

Stage 2



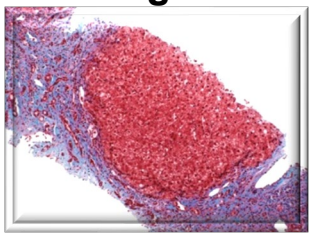
Fibrous expansion of most portal areas with occasional portal to portal bridging

Stage 3



Fibrous expansion of portal areas with marked bridging (portal-to-portal and portal-to-central)

Stage 4



Cirrhosis

Cirrhotic Liver

Faria SC, et al. *Radiographics.* 2009;29:1615-1635. Adapted from Everson GT.

RISK BASED TESTING HAS FAILED
Candidates for Screening for HBV?
HBV FOUNDATION : >>>>>EVERYONE

- Persons born in high and intermediate endemic areas (≥2% prevalence)
- US born children of immigrants from high-risk areas
- Household and sexual contacts of HBsAg-positive persons
- Persons who have ever injected drugs
- Persons with multiple sexual partner, or history of STDs
- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT/AST
- Individuals infected with HIV or HCV
- Patients undergoing dialysis
- All pregnant women

Weinbaum CM, et al. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.
LeFevre ML on behalf of the U.S. Preventive Services Task Force. *Ann Intern Med.* 2014;161:58-66.

Rationale for Prompt Identification of HBV-Infected Persons: Test all adults

Implement important interventions to reduce morbidity and mortality

- Clinical evaluations to detect onset and progression of HBV-related liver disease
  - HBV DNA, HBeAg, ALT, HCC biomarker panel, imaging, APRI, FIB-4, transient elastography
- Antiviral therapy can delay or reverse progression of liver disease
- Detect HCC at a potentially treatable stage with baseline AFP and periodic ultrasound/biomarker surveillance
- Stop transmission
- Implement interventions to reduce progression of liver injury
  - Hepatitis A vaccination
  - Counseling to avoid excessive alcohol use
  - Manage MAFLD

Adapted from Weinbaum CM, et al. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.
Chaiteerakij R, et al. *Clin Gastroenterol Hepatol.* 2015;13:237-245.

How do we arrive at: WHO Hepatitis Elimination Targets?

Target areas			Baseline 2015	2020 target	2030 target
Service coverage	Prevention	1 Three-dose hepatitis B vaccine for infants (coverage %)	82%	90%	90%
		2 Prevention of mother-to-child transmission of HBV: hepatitis B birth-dose vaccination or other approaches (coverage %)	38%	50%	90%
		3 Blood and injection safety (coverage %) — Blood safety: donations screened with quality assurance	89%	95%	100%
		3 Blood and injection safety (coverage %) — Injection safety: use of engineered devices	5%	50%	90%
		4 Harm reduction (sterile syringe/needle set distributed per person per year for people who inject drugs [PWID])	20	200	300
	5 Treatment	5a. Diagnosis of HBV and HCV (coverage %)	<5%	30%	90%
		5b. Treatment of HBV and HCV (coverage %)	<1%	5 million (HBV) 3 million (HCV)	80% eligible treated
Impact leading to elimination	Incidence of chronic HBV and HCV infections		6–10 million	30% reduction	90% reduction
	Mortality from chronic HBV and HCV infections		1.46 million	10% reduction	65% reduction

WHO. Combating Hepatitis B and C to Reach Elimination by 2030. Geneva, Switzerland: WHO, 2016.

Key Takeaways

- As countries progress toward eliminating HCV and HBV, more work is needed to enhance political will and financing of national elimination programs

- Vaccination campaigns have successfully reduced HBV prevalence in children, in >80 countries
- Most countries have not expanded HBV and HCV treatment beyond specialists
- HBV policies seemingly lag behind HCV (no countries on track for HBV elimination)
- Expanded screening and treatment for HBV is needed

Updated evaluation of global progress towards HBV and HCV elimination, preliminary data through 2021

Sarah Blach

AASLD 2022, Washington DC

Occult HBV Infection/Viremia and Occult HBV HBsAg(-) HBV DNA(+)

- Occult HBV infection/viremia
  - Presence of HBV DNA in the liver (± detectable serum HBV DNA) of individuals testing HBsAg negative by currently available assays, most patients are anti-HBc positive
- Occult HBV is the preferred term when the level of infectivity can not be established
  - Detection of HBV DNA does not always correspond to infectivity or to the number of progeny viruses released from hepatocytes
  - Prevalence varies significantly between geographic regions, various patient populations tested, and type of routine screening assay used
  - Detection requires assays with a lower limit of detection of <10 IU/L for HBV DNA and <0.1 ng/mL for HBsAg
  - Relatively common among HCV-infected patients
  - Transmission via solid organ transplantation or transfusion has been reported
  - Reactivation can occur with immunosuppression or intensive cytotoxic chemotherapy

Torbenson M, et al. *Lancet Infect.* 2002;2:479-486.
Hollinger FB, et al. *J Viral Hepat.* 2010;17:1-15.

Natural History of HBV and Treatment Indications

Parameter	HBeAg Positive		HBeAg Negative		Resolved HBV infection
	Chronic *Infection*	Chronic *Hepatitis*	Chronic *Infection*	Chronic *Hepatitis*	
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative, anti-HBc positive
HBsAg	High	High/intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	> 10^7 IU/mL	10^4 to 10^7 IU/mL	< 2000 IU/mL*	> 2000 IU/mL	Undetectable
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe	None
Disease progression	Low	**Moderate to high**	Low	**Moderate to high**	None (HCC)
Treatment	Not indicated‡	**Indicated**	Not indicated	**Indicated**	Not indicated§

*HBV DNA levels up to 20,000 IU/mL can occur without signs of chronic hepatitis. †Persistently or intermittently. ‡Treatment is indicated in some patients. § Prophylaxis for select cases.

EASL. J Hepatol. 2017;67:370.

Slide credit: clinicaloptions.com

Criteria to Start Antivirals in HBsAg+ Patient is way too complicated

- **3 criteria: ALT, HBV DNA and disease severity**

	HBV DNA	ALT	Stage	Other Factors
AASLD HBeAg+ HBeAg-	 >20,000 >2000	 ≥2XULN ≥2XULN	All with cirrhosis	Significant histologic disease +FH HCC +FH cirrhosis Extrahepatic manifestations Older age
EASL HBeAg+ or HBeAg-			All with cirrhosis	+FH HCC +FH cirrhosis Extrahepatic manifestations
	>2000	≥ULN	Moderate disease	
	>20,000	≥2XULN	Any disease	
APASL HBeAg+ HBeAg-	 >20,000 >2,000	 ≥2 ULN ≥2 ULN	Cirrhosis if elevated ALT or HBV DNA>2000	Significant histologic disease +FH HCC +FH cirrhosis Older age

- **Thresholds are a guide, not absolute and HBVDNA is a continuous variable**
- **HBV DNA levels should be linked with risk**
- **ALT elevation should be due to HBV disease**

AASLD HBV Treatment Guideline 2018
EASL HBV Treatment Guideline 2017
APASL HBV Treatment Guideline 2015

Treat HBV 2019

- HBV DNA > 2000 and
  - ALT over 20-25 in women over 30-35 in men
  - Elevated HCC biomarkers
  - Older age and active liver disease
  - High risk for HCC, NASH, smokers
  - Family hx of HCC
- HBV DNA + cirrhosis
- HCC diagnosis
- Any patient with cirrhosis with any HBV DNA + level
- Risk of Transmission
- Pregnancy

Treat 2022

- HBV DNA+
  - (risk of HCC, cirrhosis, LT and death)
- Risk of Transmission
- Stigma
- QOL
- Pregnancy

Untreated 'Immune-Tolerant' Patients have a Significant Risk for Morbidity and Mortality

Untreated patients (n=413)
- Immune tolerant phase
- HBV DNA ≥20,000 IU/mL
- No evidence of cirrhosis
- Normal ALT levels*

Treated patients (n=1497)
- Immune active phase
- ALT levels ≥80 IU/mL
- Treated with NAs

	Untreated patients		Treated patients	
10-year risk of HCC	12.7%	2.54 x increased risk	6.1%	p=0.001
10-year risk of death/transplantation	9.7%	3.38 x increased risk	3.4%	p<0.001

Percentages represent estimated cumulative incidence. *Normal ALT females, <19 IU/mL and males, <30 IU/mL

Kim GA, et al. Gut 2018;67:945–52

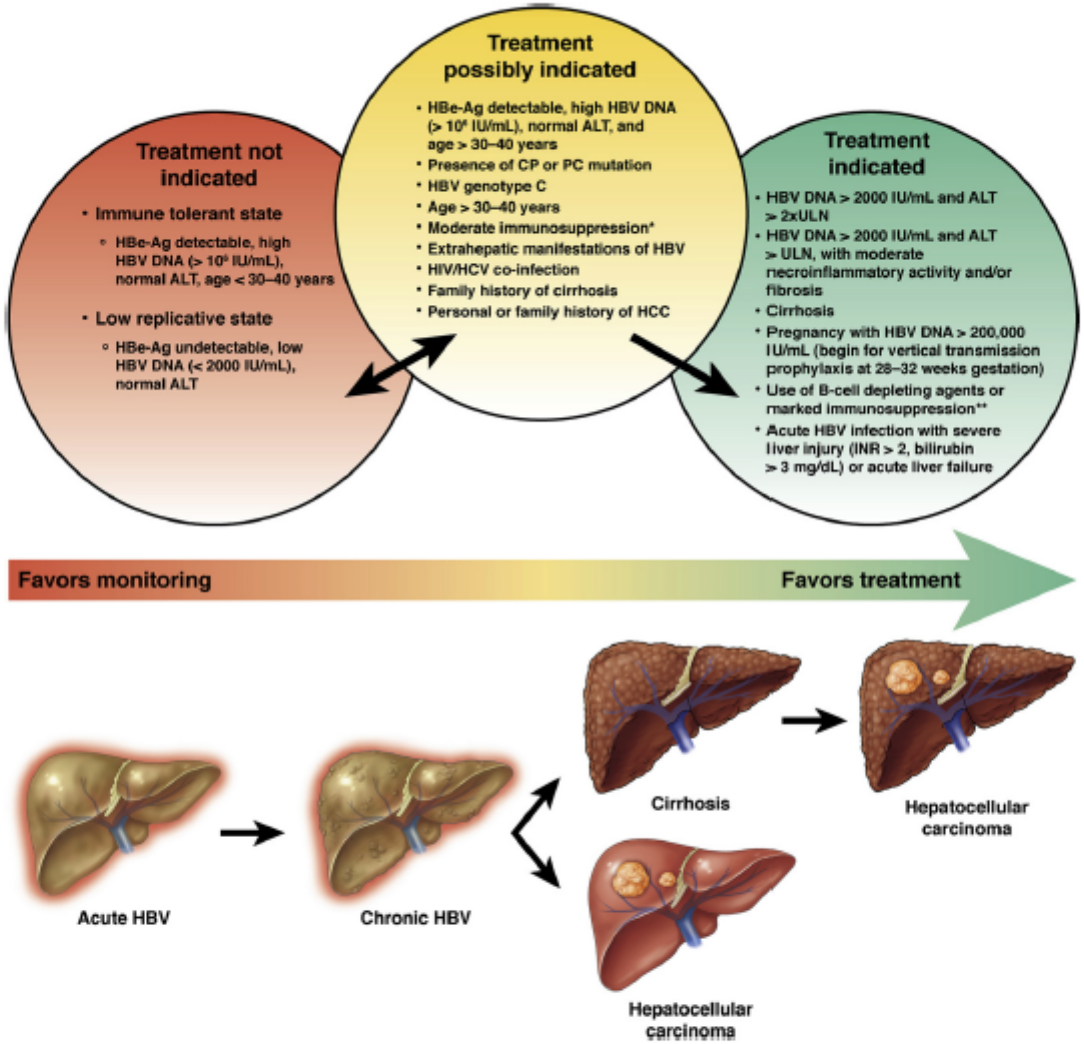


Figure 1. Treatment is indicated by evidence of significant and/or progressive fibrosis or necroinflammatory activity or in special circumstances (eg, immunosuppression, pregnancy) when the risk of adverse outcomes is especially high. ALT, alanine aminotransferase; CP, core promoter; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; PC, precore; ULN, upper limit of normal. *Examples of moderate immunosuppression include treatment with anti–tumor necrosis factor or other cytokine/integrin inhibitors, tyrosine kinase inhibitors, or less than 10 mg/day prednisone (or equivalent) for at least 1 month.[12] **Examples of marked immunosuppression include treatment with anthracycline derivatives or 10–20 mg prednisone/day (or greater) for at least 1 month.[12]

Quantitative HBsAg Levels and Risk for HCC

HBsAg Level, IU/mL	Relative Risk	95% CI
Tseng et al[1]		
< 10	1.0	
10-99	1.1	0.3-4.2
100-999	2.3	0.7-7.3
1000-9999	3.2	1.0-10.0
≥ 10,000	2.9	0.9-9.5
Lee et al[2]		
< 100	1.0	
100-999	3.2	1.7-6.1
≥ 1000	5.4	3.0-9.9

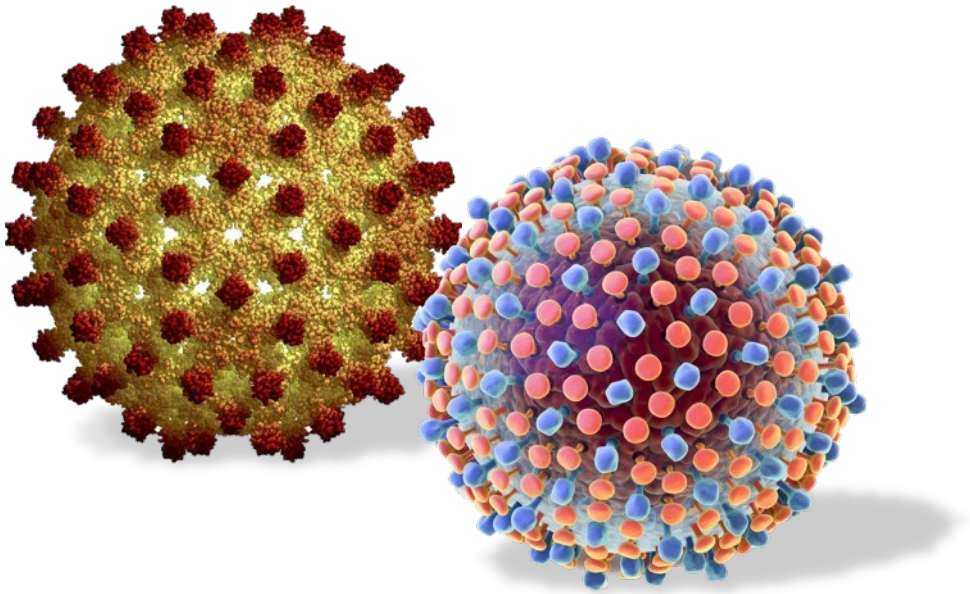
qHBsAg can also be used for establishing phase of HBV disease, infectivity, risk of cirrhosis, Natural history of disease, risk of liver cancer, treatment response

1. Tseng. Gastroenterology. 2012;142:1140.
2. 2. Lee. Hepatology. 2013;58:546.

Someone who is infected with Hepatitis B or C.

=

Someone who smokes 1 pack of cigarettes per day.

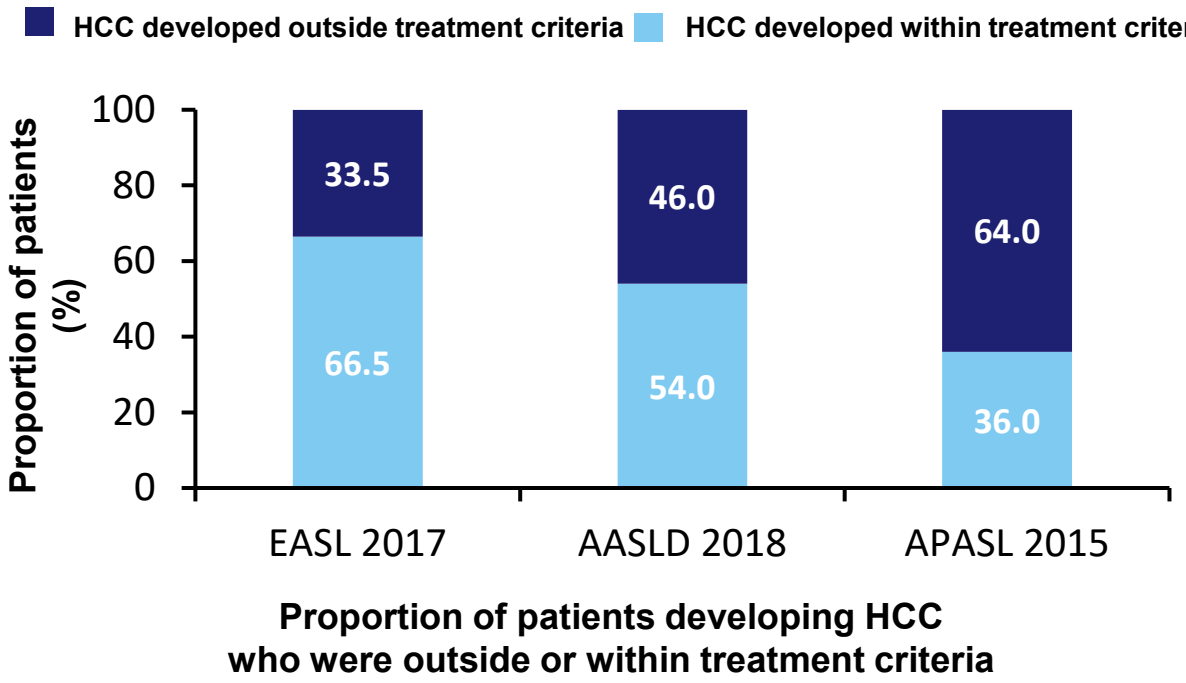


After D Razavi Polaris

Proportion of Patients Outside the International Treatment Criteria Developing HCC

Korean retrospective cohort study conducted in 3,624 treatment-naive CHB patients (median follow-up: 4.6 years)

Fewer patients developed HCC with less stringent EASL 2017 criteria



Sinn et al. J Viral Hepat. 2019

Why Treat Patients in Indeterminant Phase and "Immune Tolerant Phase"? New Term Chronic Infection

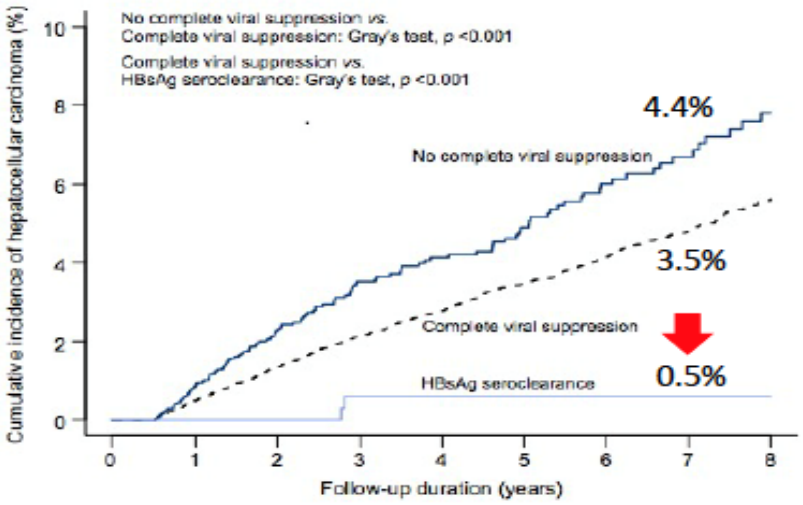
- Reduce HBV integration by treating early, hence reduce HCC risk
- By suppressing HBV DNA not only risk reduction of HCC but also of potential liver damage
- "IT" patients will later develop immune active disease where the risk is highest.

  Why not short circuit through treatment which is safe and without resistance?
- Reduce the rate of horizontal and vertical transmission
- Simplified treatment strategy to drive HBV elimination goal: Test & Treat
- Stigma
- QOL/PRO

Liver Cancer Risk: End Point Should be HBsAg Clearance

Suppression Good, HBsAg Clearance Better

Hong-Kong Cohort:
20,263 NA-treated patients with chronic hepatitis B

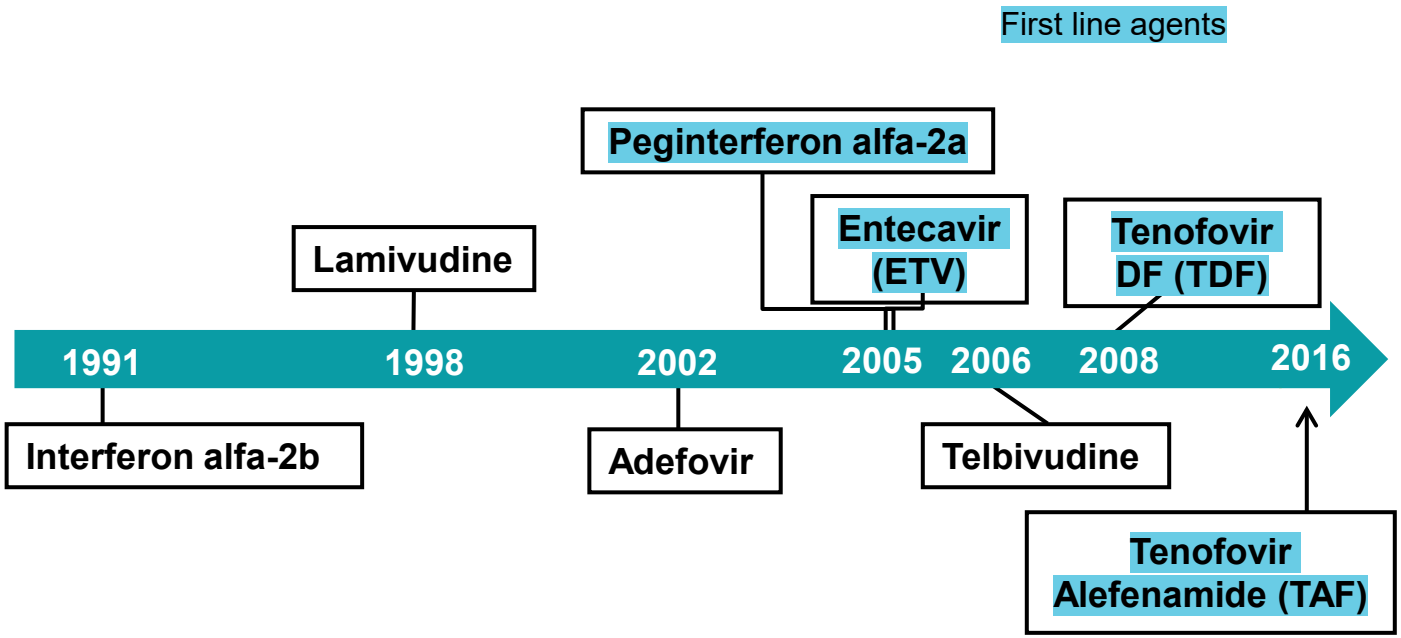


- **Median follow-up 4.8 (IQR: 2.8–7.0) yrs**
- **86.4% had complete viral suppression**
- **2.1% achieved HBsAg seroclearance**

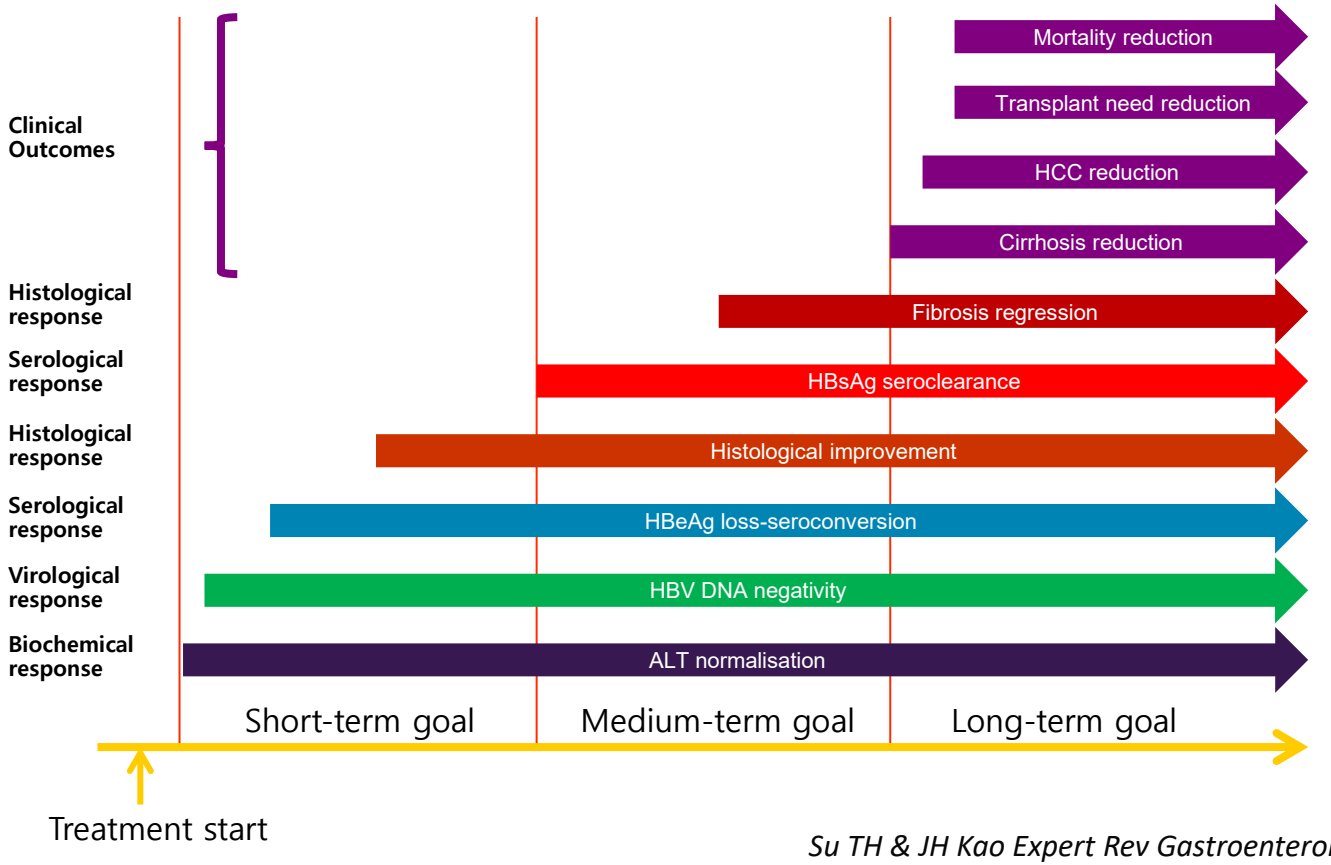
Incidence of HCC lowest in those who achieve HBsAg loss

Yip TCK, J Hepatology 2019;70:361-370

Timeline for drug HBV development



Achievements of Current Therapeutics



Su TH & JH Kao Expert Rev Gastroenterol Hepatol 2015;9:141-54

Low Rate of Functional Cure by Existing Treatment

Nucleos(t)ide Analogs

Cumulative HBsAg seroclearance by entecavir: 3.5%

Drug	HBsAg
Entecavir	2.5% (7 y
TDF	11.8% for HBe HBeAg⁻ (7
TAF	NA

MF et al., Nat Rev Dis Primers. 2018;4:18035

PEG - IFN

2.4% at 5 years (n= 85, HBe

8% at 3 years (n=230, HBeAg-

Wong V et al. Hepatology 2010;51(6):1945-53
Marcellin P et al. Gastroenterology 2009; 136(7):2169-79

Long-term treatment

We Never Say "Life-long" or indefinite

We give our patients hope with over 30 new medications In development and > 10 antiviral targets

Indications for Selecting ETV or TAF Over TDF*

- In some circumstances ETV or TAF may be a more appropriate treatment choice than 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

*TAF should be preferred to ETV in patients with previous exposure to NAs; †ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged ≥12 years and ≥35 kg body weight) with estimated CrCl ≥15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.

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

TDF versus TAF: What is the Difference?

TDF

- Tenofovir disoproxil fumarate
- 300 mg tenofovir
- Less efficient delivery to liver
- Greater systemic exposure
- Equivalent antiviral efficacy
- Defined renal and bone tox risk

TAF

- Tenofovir alafenamide
- 25 mg tenofovir
- More efficient delivery to liver
- Less systemic exposure
  - Much less bone and renal risk
- Equivalent antiviral efficacy
- Better ALT suppression

Monitoring Patients Treated With ETV, TDF or TAF

- Periodical monitoring and long-term surveillance is required in patients

Recommendations (monitoring)
ALT and serum HBV DNA*
• All patients treated with NAs q3-4 months for first year then q6 months
Renal monitoring†
• Patients at risk of renal disease treated with any NA
• All patients treated with TDF, regardless of renal risk
Switch to ETV or TAF‡
• Should be considered in patients on TDF at risk of development of and/or with underlying renal or bone disease
Recommendations (long-term surveillance)
HCC surveillance recommended
• All patients under effective long-term NA therapy
HCC surveillance mandatory
• All patients with cirrhosis or with moderate or high HCC risk scores at the onset of NA therapy

*Liver function tests should be performed every 3–4 months during the first year and every 6 months thereafter. Serum HBV DNA should be determined every 3–4 months during the first year and every 6–12 months thereafter; †Including at least eGFR and serum phosphate levels. Frequency of renal monitoring can be every 3 months during the first year and every 6 months thereafter, if no deterioration. Closer renal monitoring is required in patients who develop CrCl <60 ml/min or serum phosphate levels <2 mg/dl; ‡Depending on previous LAM exposure.
EASL CPG HBV. *J Hepatol.* 2017;67:370–98.

Last Updated July 19, 2019

Hepatitis B Management: Guidance for the Primary Care Provider

Purpose of Guidance: The purpose of this document is to provide simplified, up-to-date, and readily accessible guidance for primary care medical providers related to the prevention, diagnosis, and management of hepatitis B virus (HBV) infection, including hepatocellular carcinoma surveillance.

About the HBV Primary Care Workgroup: This guidance was developed by the Workgroup on Hepatitis B Guidance for the Primary Care Provider. This workgroup consists of a multidisciplinary panel of national experts in the field of viral hepatitis, including representation from hepatology, infectious diseases, primary care, public health, and other national organizations. The workgroup was organized by the National Taskforce on Hepatitis B in partnership with the San Francisco Bay Area Hep B Free Campaign and Project ECHO™ and did not receive any outside funding.

Collaboration with University of Washington
These guidelines were produced in collaboration with the University of Washington's National Viral Hepatitis Project team. The University of Washington team will produce and post a pdf version and an interactive version of this guidance on the University of Washington's Hepatitis B Online website (currently under development), with an anticipated launch in the fall 2019. The *Hepatitis B Online* (hepatitisB.uw.edu) is a free educational resource funded by the Centers for Disease Control and Prevention (CDC).

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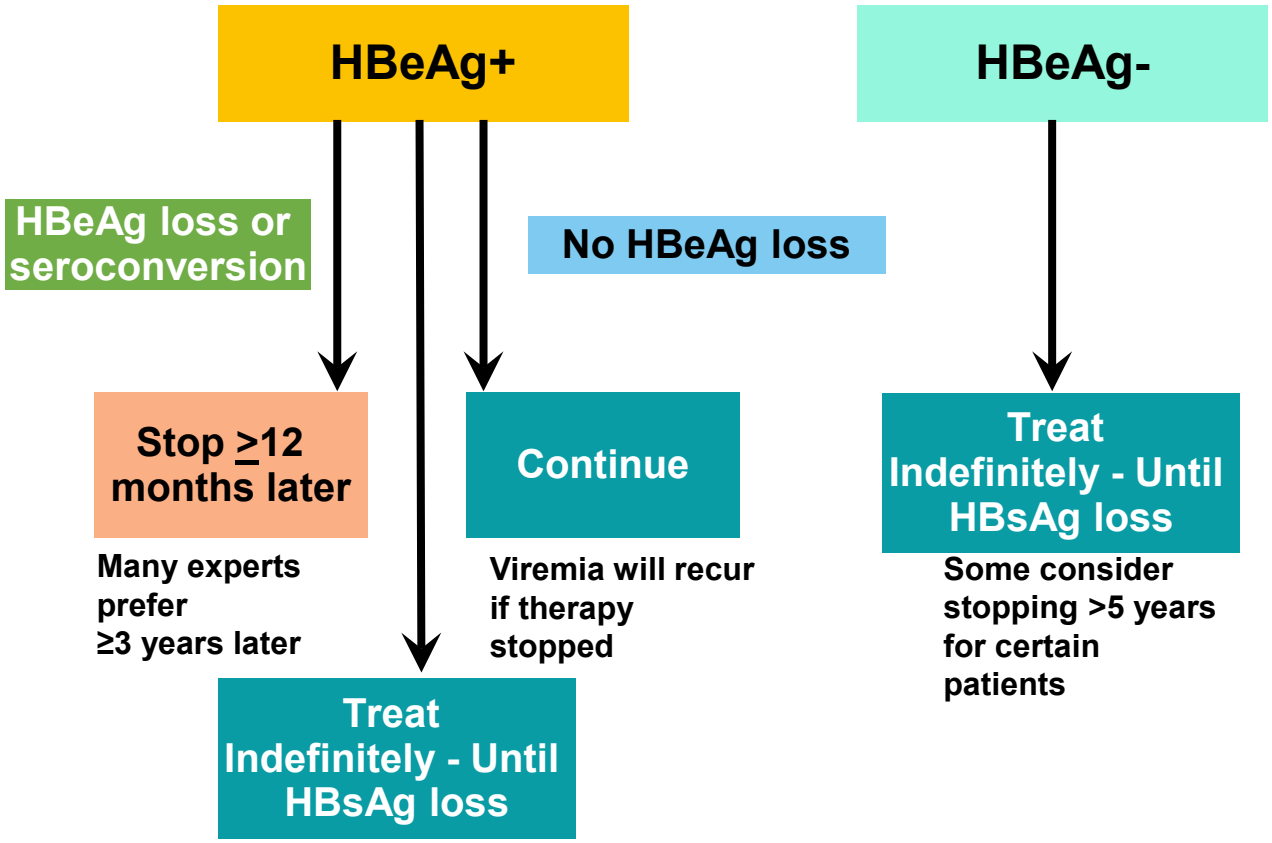
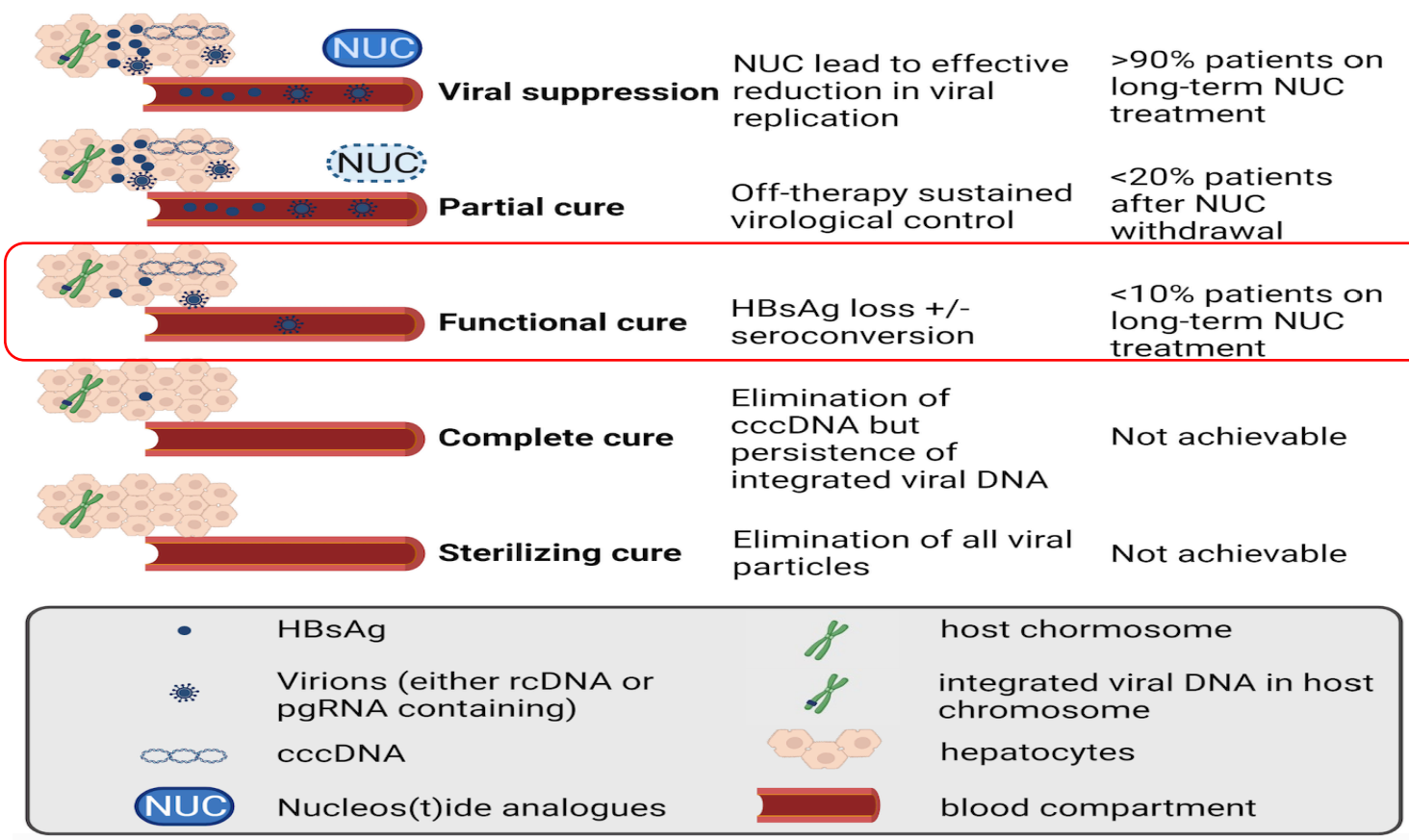
Treatment Endpoints



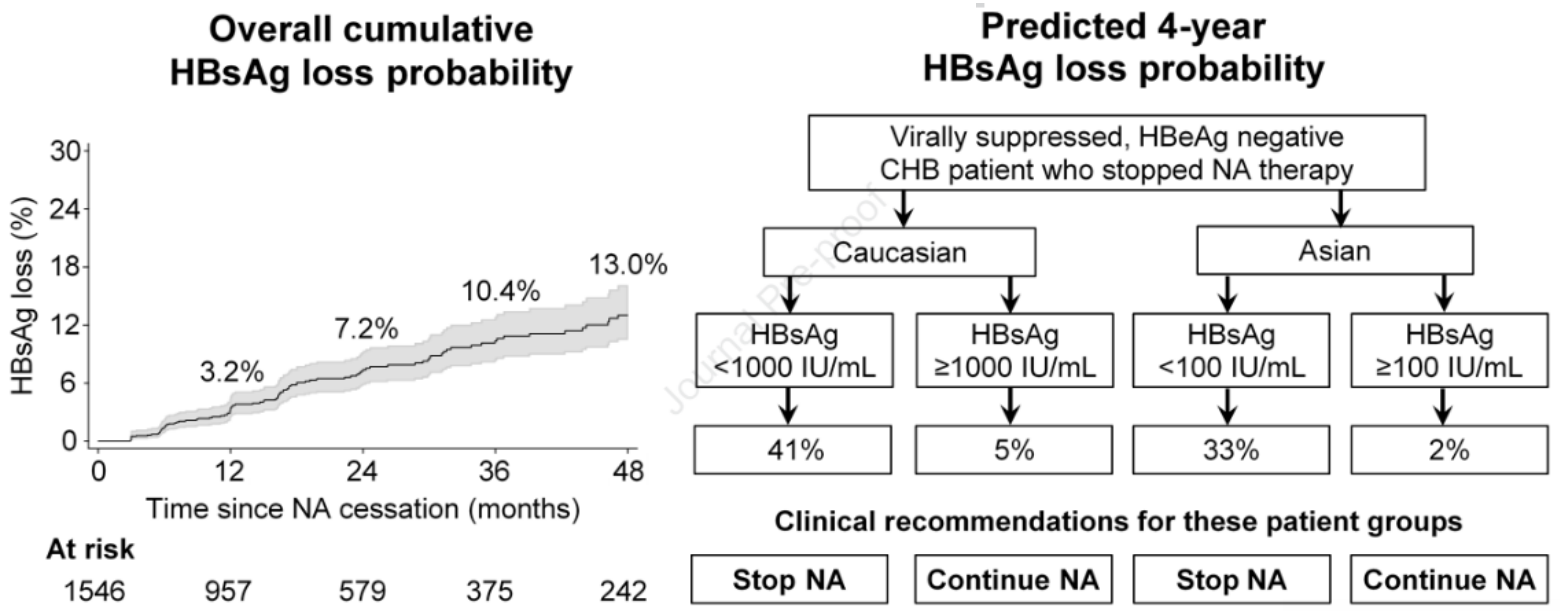
- Can stop therapy if HBsAg clearance documented for ≥6 months
- Late reappearance of HBsAg very uncommon even without anti-HBs

Treatment Goals for Chronic Hepatitis B



Mak LY…Yuen MF. Trends in Mol Med 2022;28:742-57

RETRACT-B Study: Long Term Outcomes After Stopping Nucs and a Treatment Algorithm Based on qHBsAg

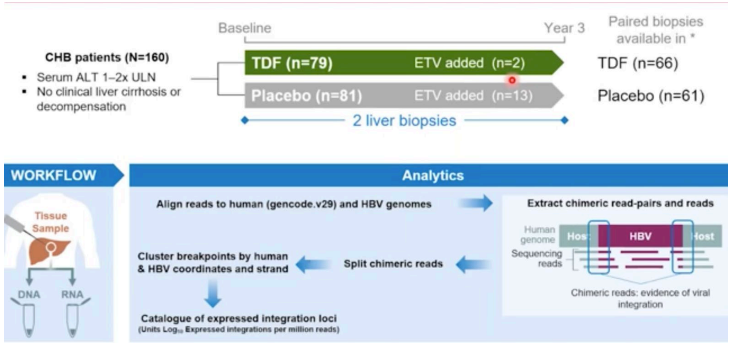


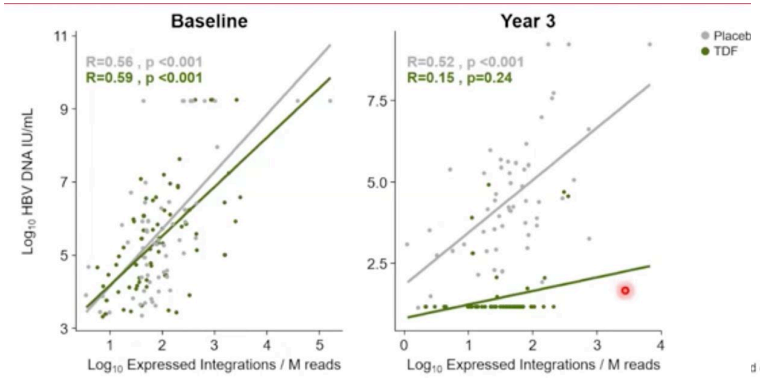
Hepatic decompensation after NA cessation:

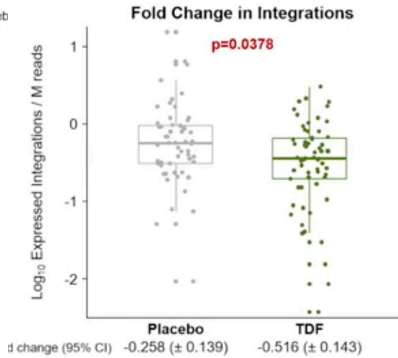
- With cirrhosis: 4.3%
- Without cirrhosis: 0.8% patients

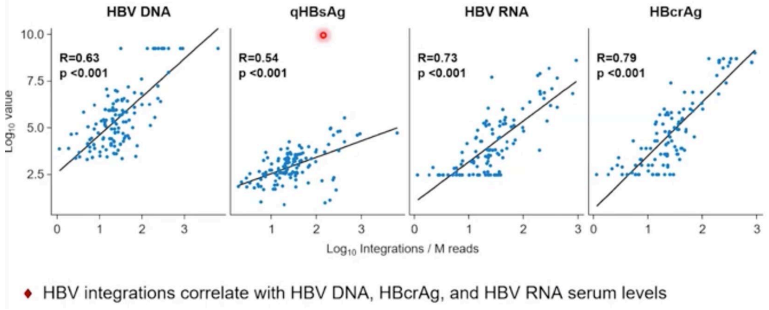
Hirode G et al, Gastroenterology 2021;https://doi.org/10.1053/j.gastro.2021.11.002

Tenofovir Disoproxil Fumarate Treatment Reduces the Number of Transcriptionally Active Viral Integrations in CHB







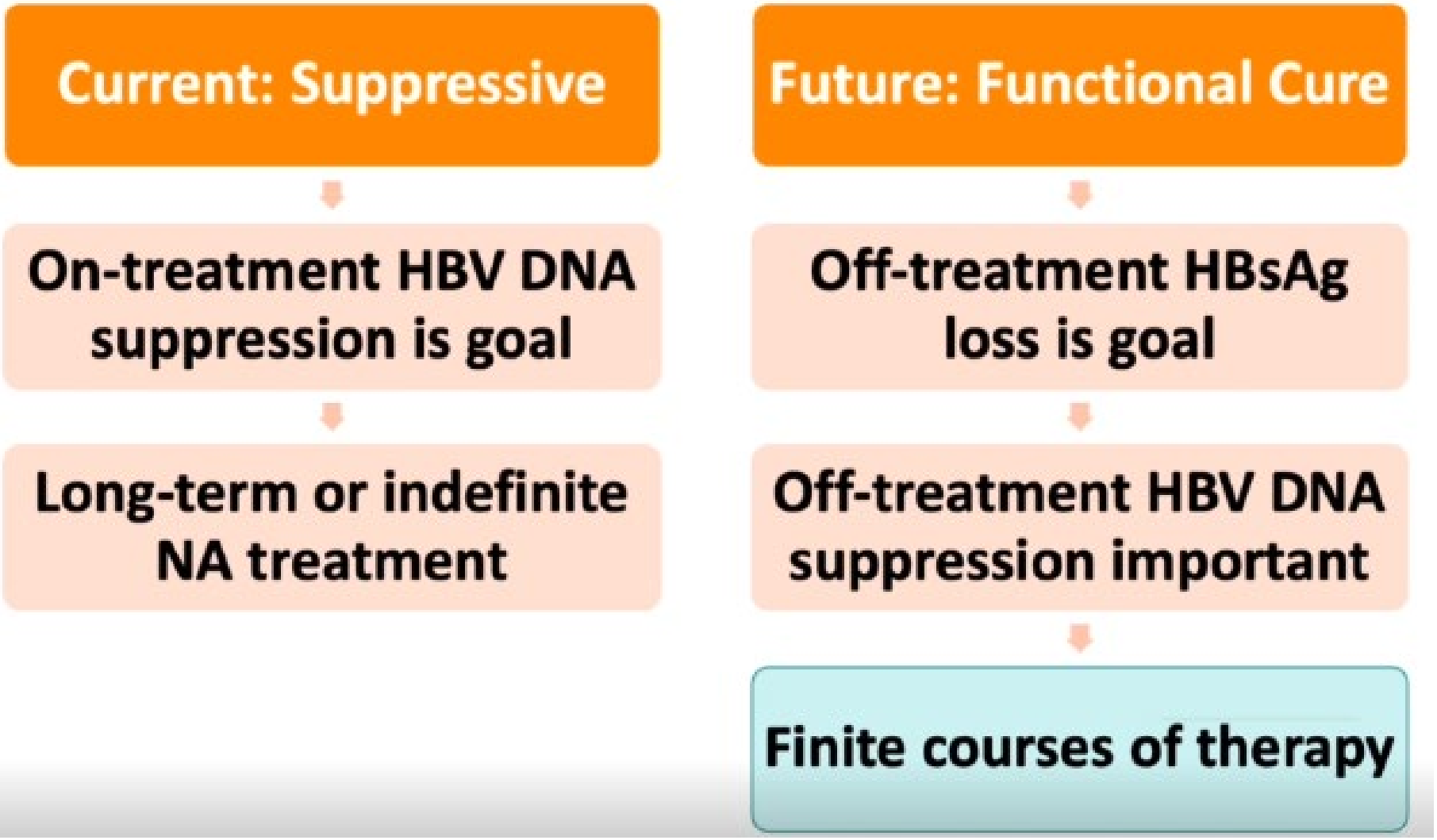


Reduction in viral load with TDF is associated with with reduced expressed viral integrations and dysregulated genes

Similar results found by Chow et al (AASLD 2020)

Yao-Chun Hsu et al. AASLD 2020

HBV Treatment Paradigm is Changing



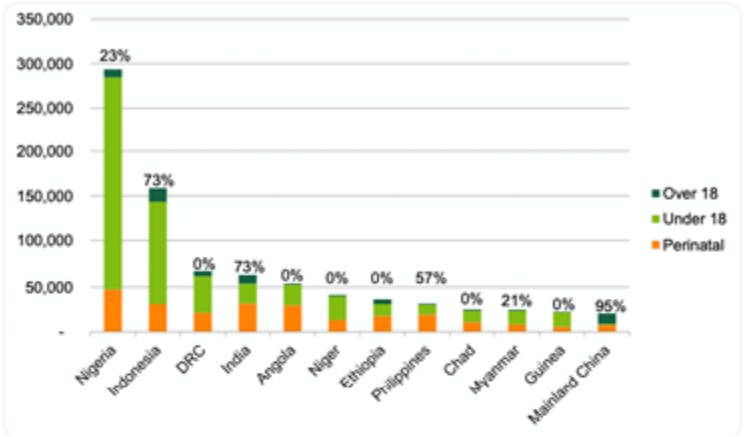
HBV Vaccination

- Strategies to fight HBV infection
  - Treat patients with chronic HBV infection
  - Interrupting the route of transmission
  - Immunize susceptible individuals
  - Birth dose of HBV vaccine <24 hours from birth preferably < 12 hours, ideally < 2 hours (With HBIG if mother is HBsAg+)
- Vaccination is the most effective strategy to prevent individuals from contracting HBV infection
- Preferred vaccines is/are Heplisav-B, 2 dose regimen, great safety, efficacy and compliance or VBI 3 dose triple antigen vaccine

Locarnini S, et al. *J Hepatol.* 2015;62(suppl):S76-S86.

Twelve countries account for over 70% of the global incidence of chronic HBV in 2022

- Only China has >90% coverage of timely birth dose
  - Half of these countries have not introduced birth dose



AASLD
The Liver

Key Takeaways

- Vaccination remains the best prevention tool that we have
- All catch-up campaigns will reduce the incidence of chronic HBV
- Vaccination in childhood reduces transmission when individuals are most vulnerable to chronic infection

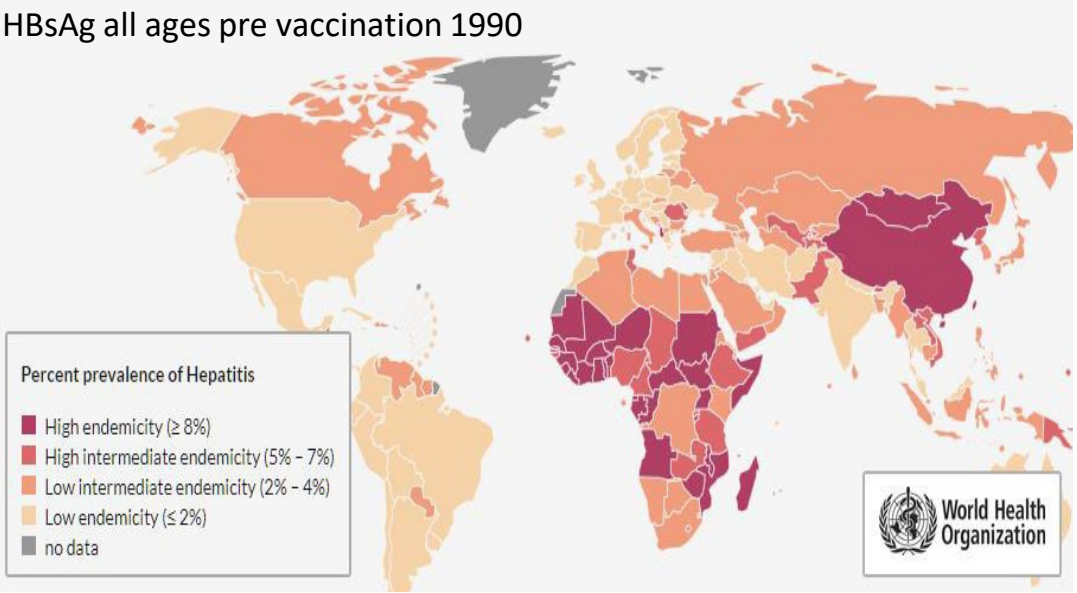
- We need to continue to strengthen prevention of mother to child transmission programs
- Catch-up campaigns among pediatric populations will have the biggest impact on chronic incidence in most of the world

D Razavi-Shearer
AASLD 2022

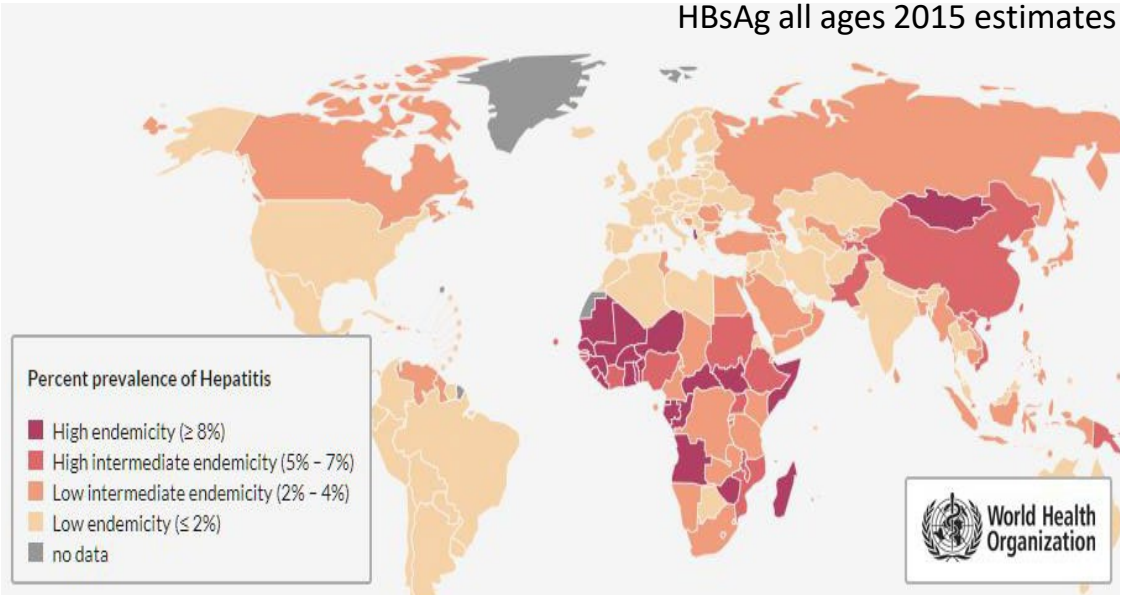
HBsAg prevalence estimates:

All ages: Vaccine is making a difference

HBsAg all ages pre vaccination 1990



HBsAg all ages 2015 estimates



Guidelines: HBV Infection and Pregnancy

- All pregnant women should be screened for HBV[1]
- Risk of chronic HBV infection linked to age of exposure; ~90% infants, 5% adults[2]
- HBIG and HBV vaccine should be administered to newborns of HBsAg-positive mothers <12 hr after delivery[1]
- HBV therapy should be discussed with expectant mothers[1]
- HBV flares are uncommon in pregnancy (~9%)[3]

1. Terrault. Hepatology. 2018;67:1560. 2. Weinbaum. MMWR Recomm Rep. 2008;57:1.
3. Chang. Am J Gastroenterol. 2016;111:1410.

#1: Can we prevent vertical transmission of HBV in highly viremic mothers with HBV vaccination plus oral TDF without HBIG?

Background

Maternal TDF therapy is recommended for highly viremic mothers with CHB (HBV DNA >200,000 IU/mL) in combination with Vaccine + HBIG → HBIG not available in many resource-limited regions with high HBV prevalence

Methods

- Multicenter RCT in China: randomized 280 HBeAg+ CHB mothers with DNA >200,000 IU/mL to receive:
  - Control group: TDF 300 mg QD Wk 28 (to delivery) + Vaccine + HBIG
  - Experimental group: TDF 300mg QD Wk 16 (to delivery) + Vaccine
- Primary endpoints: congenital defect rates and MTCT at infant age week 28

Main Findings

- N=280 (265 mothers completed) – median TDF duration of 23 wk (experimental) vs 11 weeks (control) (p<0.001) and median maternal DNA at delivery was lower in experimental (log 2.4) vs. control group (log 3.6) (P<0.001)
- Congenital defect rates were similar between experimental (3/132 =2.3%) vs control (9/142=6.3%) groups (p=0.22)
- Per-protocol analysis revealed 0% MTCT in both experimental and control groups
- Other maternal and infant safety parameters were similar between groups.

Conclusions

Maternal TDF therapy Wk 16 (to delivery) plus vaccine may be associated with similarly low rate of MTCT as SOC TDF Wk 28 (to delivery) + Vaccine + HBIG with public health implications in resource-limited settings

Table 1. Maternal variables at baseline and infant characteristics at birth

Maternal Variables, median [IQR] #	*Entire cohort (n=280)*	*Experimental (n=140)*	*Comparator (n=140)*
Age at enrollment – year	28.22 ± 3.09	28.41 ± 3.15	28.02 ± 3.03
Gravidity – No.	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)
HBV DNA – $\log_{10}$ IU/ml	8.23 (7.98, 8.42)	8.23 (7.92, 8.42)	8.23 (8.02, 8.40)
Alanine aminotransferase – U/l	20.15 (16.00, 28.90)	20.40 (16.00,31.68)	20.00 (15.05, 28.00)
eGFR – ml/min	189.55 (166.14, 214.45)	188.81 (165.21, 213.95)	190.73 (166.47, 216.53)
Infant Characteristics at Birth #	*n=273*	*n=131*	*n=142*
Male sex – No. (%)	133/273 (48.7)	59/131 (45.0)	74/142 (52.1)
Body weight <2500 g – No. (%)	9/273 (3.3)	4/131 (3.1)	5/142 (3.5)
Body length – cm	50.00 (49.00, 50)	50.00 (49.00, 50.00)	50.00 (48.38, 50.00)
Head circumference – cm	34.00 (32.00, 34.50)	34.00 (32.00, 34.50)	34.00 (32.50, 34.00)
APGAR score at 1 min	10.00 (9.00, 10.00)	10.00 (9.00, 10.00)	10.00 (9.00, 10.00)
Detectable HBV DNA at birth – No. (%) ¶	0 / 273 (0)	0 / 131 (0)	0 / 142 (0)

When comparing variables between the experimental group and comparison group, p values were all >0.05. ¶ LLOQ = 20 IU/ml.

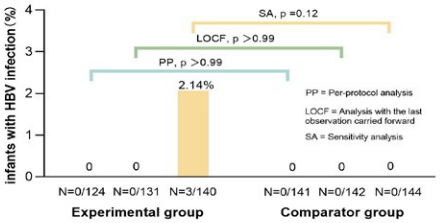


Figure 1. Mother-to-child transmission rates at the age of 28 weeks

Pan C, et al., Abstract 1.

Treatment all HBsAg positive including gray zone and "immune tolerant" HBV DNA > 6-7 $\log_{10}$ IU/ml

FOR TREATMENT

- Prevent vertical transmission
- Reduce infectivity
- Mitigate molecular damage integration events
- Reduce transition to HBeAg positive active disease
- Prevent progression to HCC
- Elimination goals met
- Improve QOL
- Reduce Stigma and discrimination
- Later add on therapies at young age?

AGAINST TREATMENT

- Spontaneous HBeAg clearance if HBeAg (+)
- Slow disease progression
- Treatment not "urgent" for those wo cirrhosis
- Resistance?
- Incomplete suppression 5%
- Unwillingness to adhere
- Guidelines do not advocate

Modified from: G Dusheiko HBF 2022

Why treat all patients who are HBV DNA+?..

- In spite of 30 years of research we have 2 patients dying every minute of HBV (800,000 patients per year)
- We are no closer to HBV elimination than we were 10 years ago
- The complexity of HBV guidelines/guidance are a barrier to treatment and a barrier to elimination as exemplified by no change in HBV linkage to care and treatment over last 10 years
- Patient reported outcomes, quality of life, are related to viral HBV DNA levels
- HBV is a stigmatizing disease
- HCC risk starts with integration and is amplified by ALT, treat early decrease integration and activity of integrants
- HBV is a blood borne infectious disease, lower viral load = less infectivity, U=U
- 1/3 of patients with “IT”/ Low/ALT high Replication have significant fibrosis
- ¼ of HBV patients have MAFLD which markedly amplifies the risk of HCC
- 1/6 of HBV patients have AUD and at risk of AALD an amplifier of HCC and cirrhosis risk
- Immune response to HBV is best at a younger age before immune tolerance or immune exhaustion evolves
- It is cost effective to treat all patient who are HBV DNA+ and may be cost savings

Simplified: 5 Line Guidelines (Pillars) of HBV for Adults

- Test all adults with HBV triple panel
- Vaccinate all adults who are triple panel negative
- HBsAg link to q DNA and anti-HDV
- Treatment: New News: treat all HBV DNA + patients including cirrhosis (Treat until HBsAg loss + 12 months consolidation)
- Surveillance for HCC and concomitant liver disease

#20: HDV prevalence in ethnically diverse, urban, safety-net populations with CHB

Background

- HDV screening is not routinely performed in patients with CHB and limited data are available which address testing practices in safety net populations

Methods

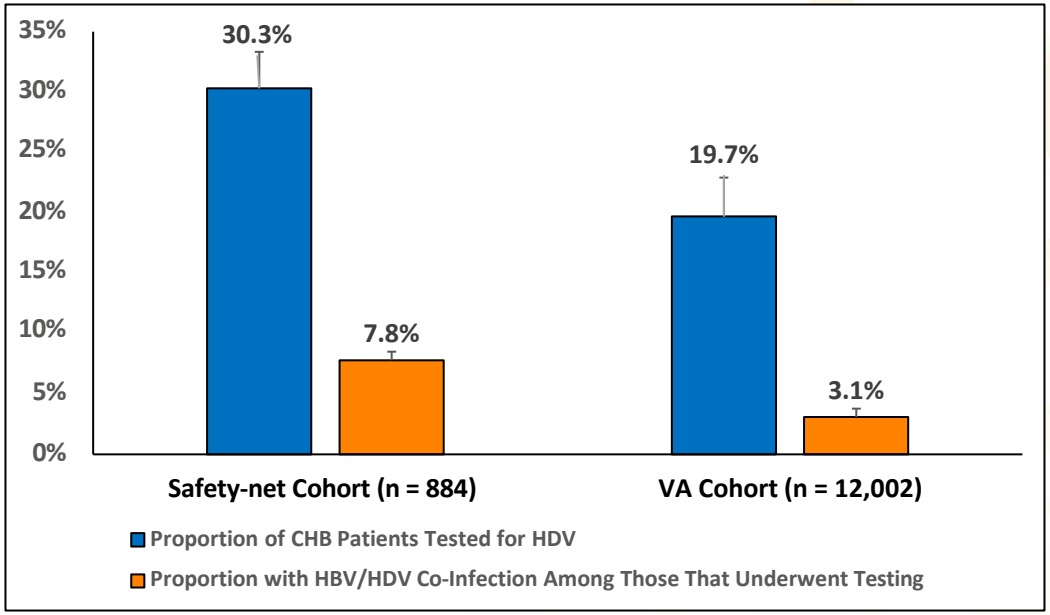
- Retrospective cohort study of two unique populations of adults with CHB from 2010 to 2021 to evaluate the proportion of patients that have been tested for HDV, and among those that were tested, the proportion with concurrent HDV infection
- To evaluate HDV testing practices and HDV prevalence among a large, urban safety-net cohort of chronic hepatitis B (CHB) patients and a national Veterans Affairs (VA) cohort of CHB patients

Main Findings

- N=884 patients with CHB in safety-net cohort (54% male, 35% AA, 29% Asian, 28% NHW, 9% HIV, 18% cirrhosis)
- HDV testing in 30.3% → 7.8% HDV positive → higher test in Asians, patients with cirrhosis, and NAFLD
- Comparison cohort (national VA): n=12,002 CHB → 19.7% testing → 3.1% HDV positive

Conclusions

- Among two distinct U.S. CHB cohorts, HDV testing ranged from 19.7% to 30.3%, and among those that underwent testing, HBV/HDV prevalence ranged from 3.1% to 7.8%.



Wong R, et al., Abstract 20.

AASLD The Liver Meeting®

#1006: Deficits in HDV care cascade (the “delta delta”)

Background

- Current AASLD guidelines recommend risk-factor based screening for HDV among patients with CHB → real-world practice patterns for HDV testing poorly described

Methods

- Retrospective cohort study of CHB cohort in New York City 2016-2021
- Examined screening, baseline characteristics, and clinical outcomes for HDV → comparison of HDV positive cases with HDV negative matched controls

Main Findings

- N=11,190 patients with CHB → 1356 (12.1%) screened for HDV, primarily by GI/hepatology specialists (90.2%) rather than IM specialists (2.7%)
- HDV seropositivity was 88/1356 (6.4%) → high risk sexual behavior and endemic country of origin were most commonly identified risk factors → 18% of cases did not meet any risk-based criteria for screening
- HDV patients more likely to have baseline cirrhosis at diagnosis (55.5% vs. 16.4%, p<0.01) → numerically more decompensation (20.8 vs 0%), HCC (15.2 vs. 5.9%) and liver transplant (20.8 vs. 0%) at follow-up but not statistically significant

Conclusions

- HDV may be underscreened in patients with CHB → not all patients with HDV had identifiable risk factors → HDV associated with higher risk of liver vents

Table 1. Baseline demographics and Outcomes Cases vs Controls

	HDV Positive n=72	HDV negative n=67	P value
Mean Age at diagnosis	48	48	(matched)
Male (%)	45 (62.5)	45 (67.2)	(matched)
Mean BMI at diagnosis (SD)	27.2 (5.2)	26.8 (4.5)	(matched)
E antigen positive (%)	7 (9.7)	6 (8.9)	(matched)
Comorbidities (%)	HCV (11.1) HIV (8.3) HLD (13.9) HTN (13.9) DM (9.7) NAFLD (6.9)	HCV (1.5) HIV (11.9) HLD (7.4) HTN (14.9) DM (16.4) NAFLD (7)	
Cirrhosis (%) at the time of HDV diagnosis	40 (55.5)	11 (16.4)	<0.01
HBV (%) suppressed	49 (68.05)	26 (38.8)	<0.01
on HBV treatment	53 (73.6)	14 (20.9)	<0.01
Significant fibrosis by FIB-4 score calculation	68%	40%	0.001
Liver decompensation- Ascites, EV, HE (%)	15 (20.8)	0	NA
Developed HCC	11 (15.2)	4 (5.9)	0.07
Needed LT	15 (20.8)	0	NA
Death	2	2	0.94

Abbreviations: HDV= hepatitis D virus; BMI= body mass index; SD= standard deviation; HCV= hepatitis C virus; HIV= human immunodeficiency virus; HLD= hyperlipidemia; HTN= hypertension; DM= diabetes mellitus; NAFLD= non-alcoholic fatty liver disease; HBV= hepatitis B virus; FIB 4= fibrosis 4; EV= Esophageal varices; HE= Hepatic encephalopathy, HCC= Hepatocellular carcinoma, LT= Liver transplantation

Nathani R, et al., Abstract 1006.

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Nathani R, et al., Abstract 1006.

LB5013: Extension of Bulevirtide Monotherapy to 72 Weeks in HDV Patients with Compensated Cirrhosis: Efficacy and Safety from the Italian Multicenter Study (HEP4Di)

Objective

- To investigate long-term real-world efficacy and safety of bulevirtide beyond 48 weeks

Methods

- HDV patients with CC were treated with BLV 2 mg SC qd up to 72 weeks

Main Findings

- N=87 patients with compensated cirrhosis under NUC were included: age 52, 52% male, BMI 25, LSM 17.4, 54% varices, 53% prior IFN, 9% active HCC
- Virologic response (HDV RNA 2 log decline vs baseline): achieved by 14%, 49%, 71%, 67%, 69% at weeks 8, 16, 24, 48, and 72, respectively
- HDV undetectable: 8%, 23%, 33% at weeks 24, 48, and 72, respectively
- Combined response (virological + biochemical): 54%, 67%, 62% at weeks 24, 48, and 72, respectively
- Platelets, LSM, HBsAg levels were stable throughout treatment – two patients underwent liver transplantation during BLV treatment (Wk 64, Wk 72) due to HC and hepatic decompensation following portal vein thrombosis

Conclusions

- BLV appears to have favorable safety and efficacy at durations 48-72 weeks.

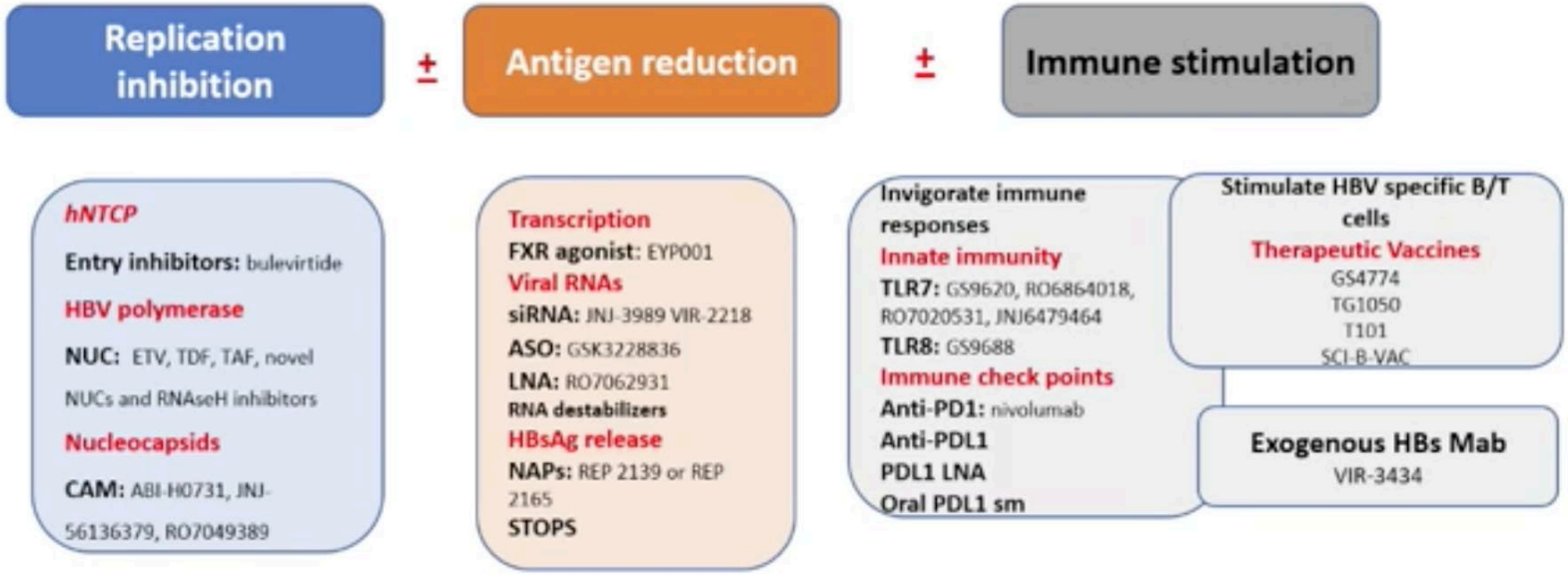
FULL PRESENTATION
AT LATE BREAKING
ORAL ABSTRACT
SESSION 3

TUE NOVEMBER 4, 2022
BALLROOM ABC
10:00-11:00 AM EST

Anolli MP, et al., Late Breaker Oral Abstract 5013.

AASLD The Liver Meeting®

The HBV drug pipeline and the potential for combination therapy to cure HBV



Fanning et al. Nat Rev Drug Discov. 2019; Revill et al, Nat Rev Gastroenterol Hepatol 2019; Roca Suarez et al, Liver International 2021

Reference site:
www.hepb.org/treatment-and-management/drug-watch/

Summary of Results

- VIR-2218 alone or in combination with PEG-IFNα was generally well-tolerated
  - Majority of TEAEs were Grade 1 or 2
- Ten participants across all cohorts receiving VIR-2218 and PEG-IFNα achieved HBsAg seroclearance by Week 48
  - 9 of the 10 participants achieved anti-HBs levels >10 mIU/mL
- Longer duration of concurrently initiated VIR-2218 and PEG-IFNα regimen (Cohort 5) resulted in
  - 30.8% participants achieved HBsAg seroclearance and anti-HBs seroconversion
  - Deepest mean HBsAg reductions (-2.9 Log_{10} IU/mL) at EOT

Abbreviations: anti-HBs, hepatitis B surface antibody; EOT, end of treatment; HBsAg, hepatitis B surface antigen; PEG-IFNα, pegylated interferon alfa-2a; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Key Takeaways

- Longer duration (48 weeks) of VIR-2218 with PEG-IFNα treatment achieves higher rates of HBsAg seroclearance with anti-HBs seroconversion by end of treatment (30.8%)
- Antiviral activity of VIR-2218 may be potentiated by PEG-IFNα, supporting future evaluation of combination with immunomodulators
- Study is ongoing and participants are being followed further

Bepirovirsen (BPV) in patients with chronic hepatitis B virus (HBV) infection controlled by nucleos(t)ide analogue therapy: HBV DNA and HBsAg loss 6 months after end of BPV treatment (B-Clear study)

Presented by Man-Fung Yuen on behalf of the B-Clear Study Group

Bepirovirsen 300 mg x 24 weeks (Arm 1) and bepirovirsen 300 mg x 12 weeks + 150 mg x 12 weeks (Arm 2) both resulted in **9% of participants achieving HBsAg and HBV DNA loss maintained for 24 weeks** after bepirovirsen end of treatment without newly initiated antiviral treatment.

- The proportions of participants who met the modified primary outcome (allowing unconfirmed increases in HBsAg and/or HBV DNA) were similar.

Participants with **low baseline HBsAg** were more likely to achieve the primary outcome than those with high baseline HBsAg.

- In Arm 1, 16% participants with baseline HBsAg ≤3 log10 IU/mL achieved the primary outcome.
- Except for BMI, other covariates did not appear to be independent predictors of response.

Most ALT increases occurred in association with HBsAg decline.

Bepirovirsen 300 mg weekly for 24 weeks did not demonstrate any marked difference in safety profile or decreased tolerability compared with the other bepirovirsen regimens investigated.

Additional results for the B-Clear Not-on-NA population are presented in poster 5022.

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; OT, off treatment; LLOD, lower limit of detection; ULN, upper limit of normal; W, week

Thank You!

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