Updates on Hepatitis B Coinfection: Challenging Serology and Management Approaches



Susanna Naggie, MD, MHS
Professor of Medicine
Duke University School of Medicine
Durham, NC

IAS–USA

1

Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Naggie reported serving as a scientific advisor for Vir Bio and Pardes Biosciences. (Updated May 1, 2025)

Slide 2

2

Disclosures

Previously served as scientific advisor for Vir Bio (stocks) and Pardes Biosciences. Currently serves on event adjudication committee for BMS/PRA, DSMB for PHI and NIH, and on Scientific Leadership Board for IAS-USA. Serve as Deputy Editor for CID. (Updated 05/01/2025)

Duke Clinical & Translational Science Institute

Equity in Science, Medicine, and Health | ctsi.duke.edu

3

Learning Objectives

- Describe the serologies corresponding to HBV exposure, infection, and immunity
- Identify the goals of HBV therapy
- Explain HBV prevention strategies
- Describe risk of HBV reactivation and approaches to manage this risk in setting of LAI treatment and prevention of/for HIV

Duke Clinical & Translational Science Institute

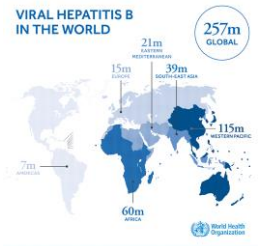
4

Hepatitis B Virus
INTRODUCTION

Duke Clinical & Translational Science Institute

5

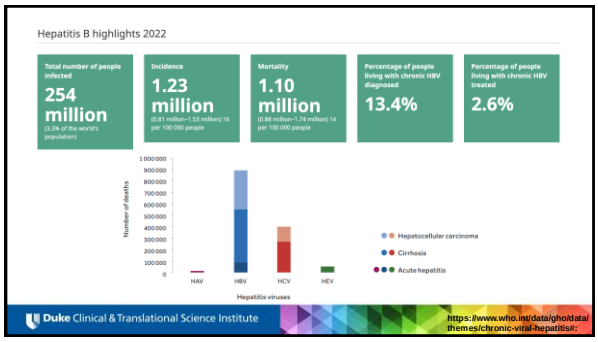
Chronic Hepatitis Global Impact



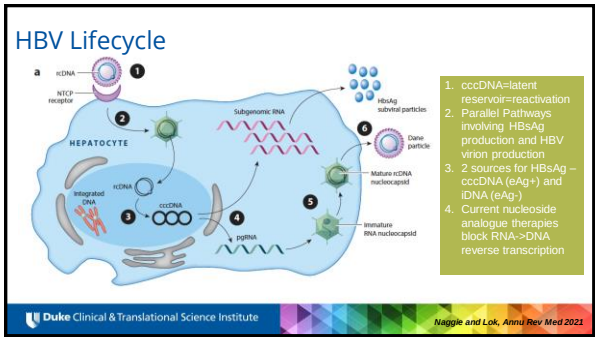
Duke Clinical & Translational Science Institute

WHO Global Hepatitis Report

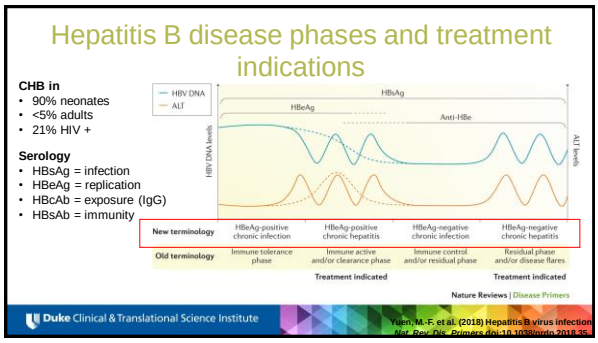
6


Hepatitis B highlights 2022
Total number of people infected
254 million
(3.3% of the world's population)
Incidence
1.23 million
(0.81 million–1.53 million) 16 per 100 000 people
Mortality
1.10 million
(0.88 million–1.74 million) 14 per 100 000 people
Percentage of people living with chronic HBV diagnosed
13.4%
Percentage of people living with chronic HBV treated
2.6%
Number of deaths
1 000 000
900 000
800 000
700 000
600 000
500 000
400 000
300 000
200 000
100 000
0
HAV
HBV
HCV
HEV
Hepatitis viruses
Hepatocellular carcinoma
Cirrhosis
Acute hepatitis
Duke Clinical & Translational Science Institute
https://www.who.int/data/gho/data/themes/chronic-viral-hepatitis#:

7

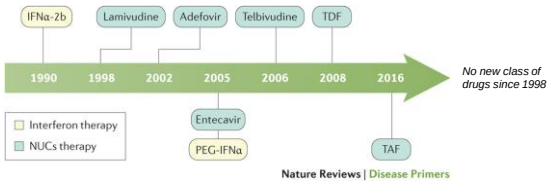

HBV Lifecycle
a
rcDNA
NTCP receptor
HEPATOCYTE
Integrated DNA
rcDNA
cccDNA
Subgenomic RNA
pgRNA
HBsAg subviral particles
Dane particle
Mature rcDNA nucleocapsid
Immature RNA nucleocapsid
1. cccDNA=latent reservoir=reactivation
2. Parallel Pathways involving HBsAg production and HBV virion production
3. 2 sources for HBsAg – cccDNA (eAg+) and iDNA (eAg-)
4. Current nucleoside analogue therapies block RNA->DNA reverse transcription
Duke Clinical & Translational Science Institute
Naggie and Lok, Annu Rev Med 2021

8


Hepatitis B disease phases and treatment indications
CHB in
• 90% neonates
• <5% adults
• 21% HIV +
Serology
• HBsAg = infection
• HBeAg = replication
• HBcAb = exposure (IgG)
• HBsAb = immunity
HBV DNA
ALT
HBsAg
HBeAg
Anti-HBe
HBV DNA levels
ALT levels
New terminology
HBeAg-positive chronic infection
HBeAg-positive chronic hepatitis
HBeAg-negative chronic infection
HBeAg-negative chronic hepatitis
Old terminology
Immune tolerance phase
Immune active and/or clearance phase
Immune control and/or residual phase
Residual phase and/or disease flares
Treatment indicated
Treatment indicated
Nature Reviews | Disease Primers
Duke Clinical & Translational Science Institute
Yuen, M.-F. et al. (2018) Hepatitis B virus infection

10

Approved agents for treating chronic HBV



Duke Clinical & Translational Science Institute

Yuen, M.-F. et al. (2018) Hepatitis B virus infection *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2018.35

11

Goals of Therapy: The Times They Might Be A-Changin'

Table 1 Therapeutic goals and definitions for current and novel HBV therapies

Therapeutic response	Blood				Liver
	ALT	HBV DNA	HBsAg	Anti-HBs	cccDNA
Virologic	N/A	Undetectable	Detected	Undetectable	Present
Biochemical	Normal	N/A	Detected	Undetectable	Present
Function cure	Normal	Undetectable	Undetectable	Detected	Present
Complete/sterilizing cure	Normal	Undetectable	Undetectable	Detected	Undetectable

Abbreviations: ALT, alanine aminotransferase; anti-HB, HBV surface antibody; cccDNA, covalently closed circular DNA; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

First line:

- Tenofovir disoproxil fumarate (generic) or Tenofovir alafenamide (not generic) – FC 8%
- Entecavir (generic) – functional cure 4-5%
- Peg IFN - significant adverse effects, no longer recommended by DHHS HIV – FC 11%

Duke Clinical & Translational Science Institute

Naggie and Lok, Annu Rev Med 2021

12

What about in HIV/HBV?

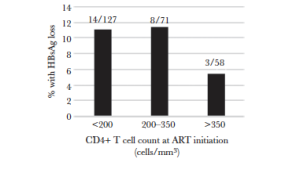


Figure 1. Percentage of human immunodeficiency virus-hepatitis B virus-coinfected patients with hepatitis B surface antigen (HBsAg) loss by 2 years of tenofovir-based therapy, by CD4 count.

- Higher than expected sAg conversion rates
- Reported relationship with CD4

Duke Clinical & Translational Science Institute

Chihota et al. JID 2020

13

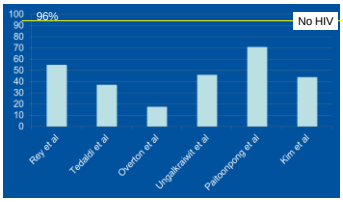
Hepatitis B Virus
PREVENTION: THIS IS THE WAY

Duke Clinical & Translational Science Institute

15

HBV PRIMARY VACCINE EFFICACY IN HIV

- HBV vaccines are HBsAg
- Recombivax HB
  - 10 or 40 mcg antigen dose
- Engerix-B
  - 20 mcg antigen dose
  - 40 mcg dose given DD
- Twinrix
  - 20 mcg antigen dose
- HEPLISAV-B (+TLR9 Agonist)
  - 20 mcg HBsAg antigen
- ~~PreHevBrio – 3 antigen adjuvant~~



Duke Clinical & Translational Science Institute

Adapted from Sun et al, WORLD J GASTRO, 2014

16

HepBCpG (HEPLISAV-B)

Approved as a 2-dose series in adults without HIV

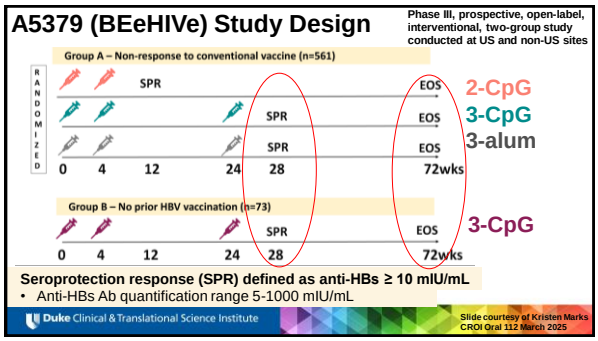
Contains CpG 1018 + recombinant HBsAg (20 mcg)

CpG 1018

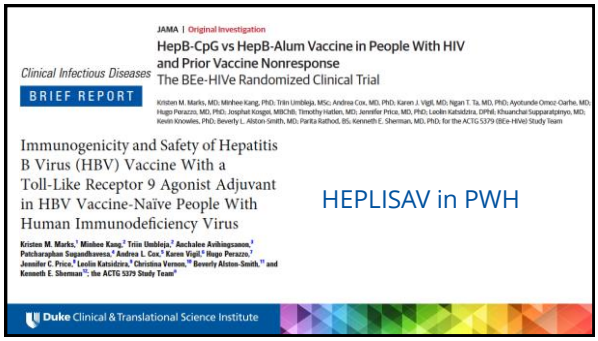
- **CpG**: 5'—C—phosphate—G—3' , that is, cytosine and guanine separated by only one phosphate group
- 22 base synthetic oligonucleotide
- Binds to TLR9 (sensing receptor for innate immune responses) expressed on dendritic cells and memory B cells)
- Leads to enhanced T and B memory for HBsAg

Duke Clinical & Translational Science Institute

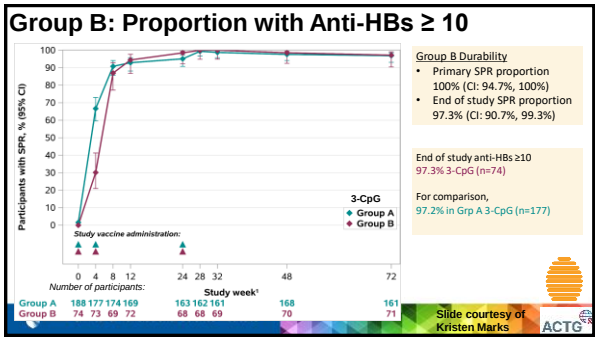
17


A5379 (BEeHIVe) Study Design
Phase III, prospective, open-label, interventional, two-group study conducted at US and non-US sites
Group A – Non-response to conventional vaccine (n=561)
RANDOMIZED
SPR
EOS
2-CpG
3-CpG
3-alum
0 4 12 24 28 72wks
Group B – No prior HBV vaccination (n=73)
3-CpG
Seroprotection response (SPR) defined as anti-HBs ≥ 10 mIU/mL
• Anti-HBs Ab quantification range 5-1000 mIU/mL
Duke Clinical & Translational Science Institute
Slide courtesy of Kristen Marks
CROI Oral 112 March 2025

18

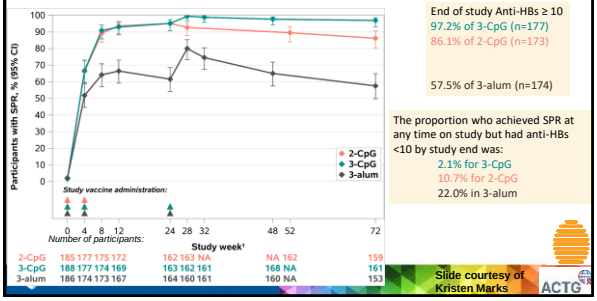

JAMA | Original Investigation
HepB-CpG vs HepB-Alum Vaccine in People With HIV and Prior Vaccine Nonresponse
The BEe-HIVe Randomized Clinical Trial
Clinical Infectious Diseases
BRIEF REPORT
Immunogenicity and Safety of Hepatitis B Virus (HBV) Vaccine With a Toll-Like Receptor 9 Agonist Adjuvant in HBV Vaccine-Naïve People With Human Immunodeficiency Virus
HEPLISAV in PWH
Duke Clinical & Translational Science Institute

19


Group B: Proportion with Anti-HBs ≥ 10
Participants with SPR, % (95% CI)
3-CpG
Group A
Group B
Study vaccine administration:
Study week¹
Number of participants:
Group A 188 177 174 169 163 162 161 168 161
Group B 74 73 69 72 68 68 69 70 71
Group B Durability
• Primary SPR proportion 100% (CI: 94.7%, 100%)
• End of study SPR proportion 97.3% (CI: 90.7%, 99.3%)
End of study anti-HBs ≥10
97.3% 3-CpG (n=74)
For comparison,
97.2% in Grp A 3-CpG (n=177)
Slide courtesy of Kristen Marks
ACTG

20

Group A: Proportion with Anti-HBs ≥ 10



End of study Anti-HBs ≥ 10
97.2% of 3-CpG (n=177)
86.1% of 2-CpG (n=173)

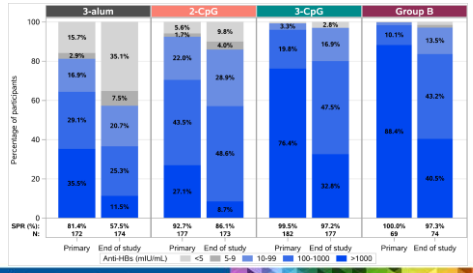
57.5% of 3-alum (n=174)

The proportion who achieved SPR at any time on study but had anti-HBs <10 by study end was:
2.1% for 3-CpG
10.7% for 2-CpG
22.0% in 3-alum

Slide courtesy of Kristen Marks

21

Group A & B: Distribution of Anti-HBs titers



Duke Clinical & Translational Science Institute

Slide courtesy of Kristen Marks

22

HBV-active ART as PrEP for HBV

- TDF/TAF > XTC (3TC or FTC) prevent incident HBV infection
- Acute HBV infections have been reported in setting of switch to LAI (PrEP/Treatment)
- Before switching to LAI, immunity to HBV should be confirmed or patients should be vaccinated

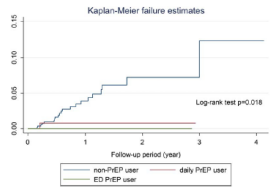


FIGURE 2 Kaplan–Meir curve to estimates incidence of HBV infection among MSM with and without PrEP. Abbreviations: ED, event-driven; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis.

Duke Clinical & Translational Science Institute

Mizushima et al, Hepatology 2023
Shilaih et al, JID 2016

23

Hepatitis B Virus

CLINICAL GUIDELINES – SPECIFIC TO HIV/HBV

Duke Clinical & Translational Science Institute

24

Primary Vaccination

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV

- Preferred - Heplisav-B IM
  - 2 shot (0, 4) wks
- 40mcg dose IM (double dose)
  - 3 shot (0, 4, 24) wks
- 20mcg dose IM (double dose)
  - 3 shot (0, 4, 24) wks
- Twinrix combined HAV and HBV
  - 3 shot (0, 4, 24) wks

Revaccination

- Preferred - Heplisav-B IM
  - 2 (0, 4) or 3 (0, 4, 24) shot
- 40mcg dose IM (double dose)
  - 3 shot (0, 4, 24) wks
- 20mcg dose IM
  - 3 shot (0, 4, 24) wks

Duke Clinical & Translational Science Institute

Lemay et al, JAMA 2011; JAMA Int Med, 2016
https://clinicalinfo.hiv.gov/en/guidelines

25

What is amnestic response in PWH and +HBcAb?

	Anti-HBs titer, IU/L			
Baseline status (no. of subjects)	1-9	10-99	100-999	≥1000
Anti-HBc negative (40)	0 (0)*	0 (0)	1 (3)	3 (8)
Anti-HBc positive (29)	6/29 (21)	3 (10)	2 (7)	2 (7)
Anti-HBc positive and anti-HBe negative (15)	6 (40)	0 (0)	0 (0)	1 (7)
Anti-HBc positive and anti-HBe positive (14)	0 (0)	3 (21)	2 (14)	1 (7)

NOTE. Data are no. (%) of subjects. Anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis Be antigen.
* $P = .004$

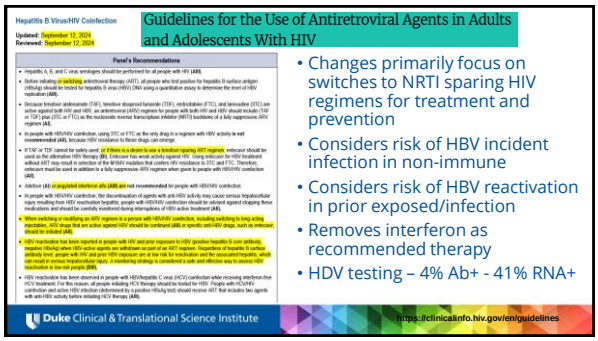
Amnestic response – 24% all HBcAb+

Amnestic Response	Week 4	Week 28 Overall	Month 18
Yes	46%	26% (58%)	19% (42%)
No	54%	--	--
Vax	89%	--	78%

Duke Clinical & Translational Science Institute

Gandi et al, JID 2005
Piroth et al, JID 2016

26



28

HBV reactivation after withdrawal of HBV-active ART

- Can occur in people with active HBV infection when active drug is withdrawn – so don't do that!
- Can occur in people with prior exposure - +HBcAb – usually "provoked"
- Risk stratification – what risk is ART withdrawal?
- High risk – rituximab
- Low risk – anti-TNF agents

Risk of HBVr	High	Intermediate	Low
HBVr rate in patients without NA prophylaxis	>10%	1-10%	<1%

Duke Clinical & Translational Science Institute

Papatheodoridis Hepatology 2022

29

Risk of HBV-active ART withdrawal

		Total number of PWH with +cAb (at risk) N=7056)	Number of cases of HBV reactivation (N=115)	Percentage of people with reactivation
Age (years)	<50 50-64 >64	1672 (24%) 4163 (59%) 1221 (17%)	35 (30%) 70 (61%) 10 (9%)	2.1% 1.7% 0.8%
Sex	Female Male	113 (1.6%) 6943 (98%)	4 (3.5%) 110 (96%)	3.5% 1.6%

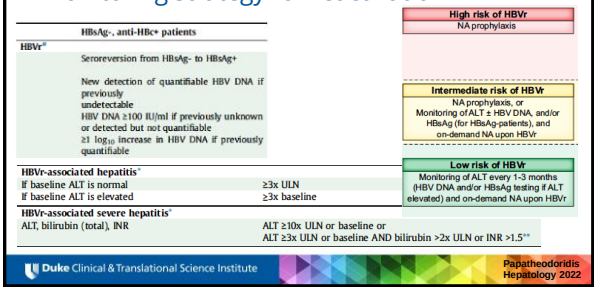
Group	+sAg ever prior	+sAb ever prior	Number at risk	Number of cases	Percentage of people
A	No	No	5925	64	1.1%
B	No	Yes	923	4	0.4%
C	Yes	No	193	40	20.7%
D	Yes	Yes	40	7	17.5%
		Total	7081	115	1.6%

Duke Clinical & Translational Science Institute

Denyer, oral abstract IDWeek 2023 OFID 2023;10 (Suppl 2)

30

Monitoring strategy for reactivation



Duke Clinical & Translational Science Institute

Papatheodoridis Hepatology 2022

31

Takeaways

- Nucleoside analogues for HBV are highly effective for treatment and prevention of HBV
- That said, adjuvanted vaccines remain our best option for prevention of HBV (infection and reactivation)
- HBcAb+ status is a risk for HBV reactivation, in HIV population with withdraw of NA (NRTI)
- Awareness and prevention of HBV reactivation is important when considering LAI for treatment or prevention

Duke Clinical & Translational Science Institute

32

Questions



Duke Clinical & Translational Science Institute

33