

Hepatitis B Virus: A Call to Action in 2024

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Disclosures or Conflicts of Interest

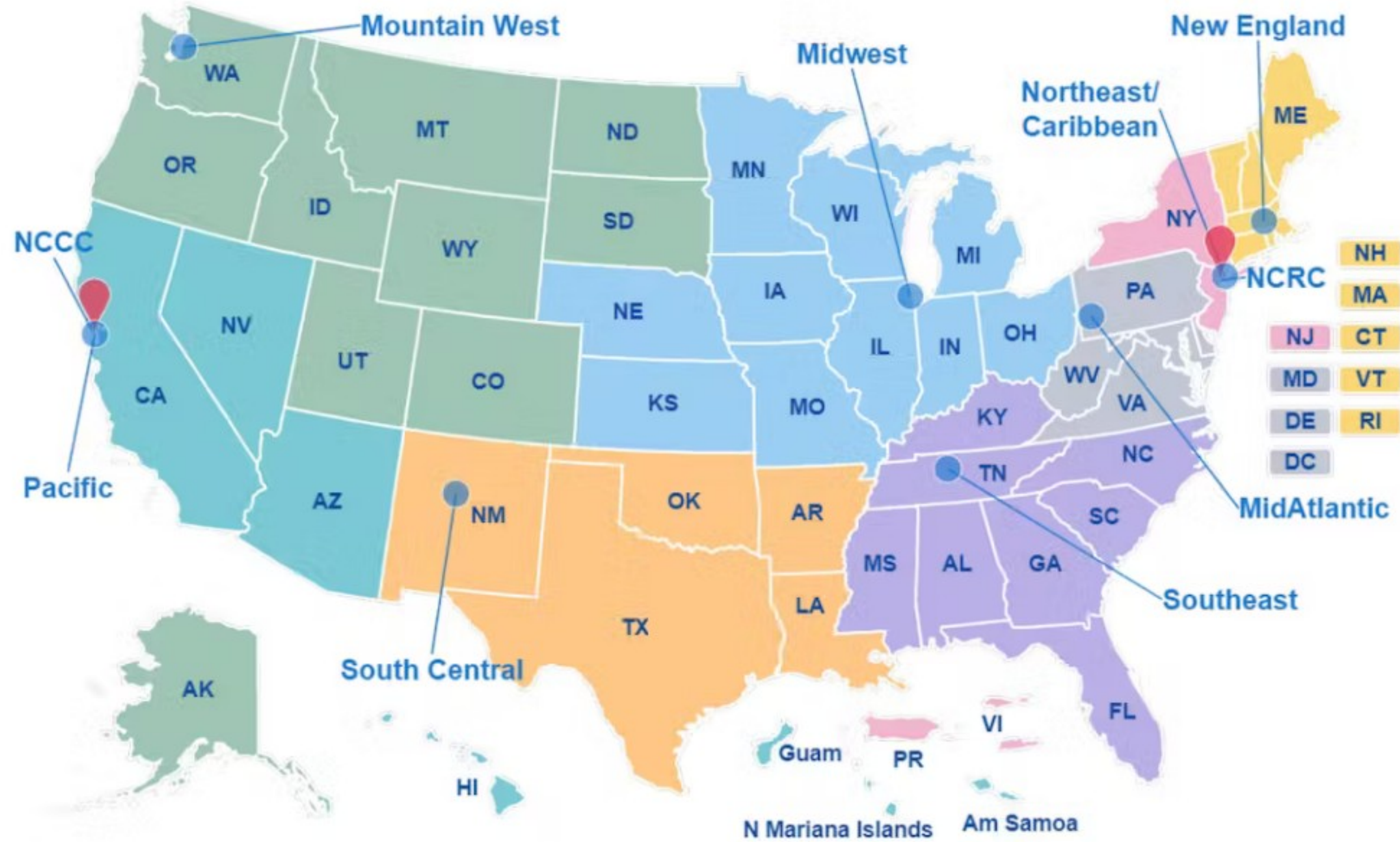
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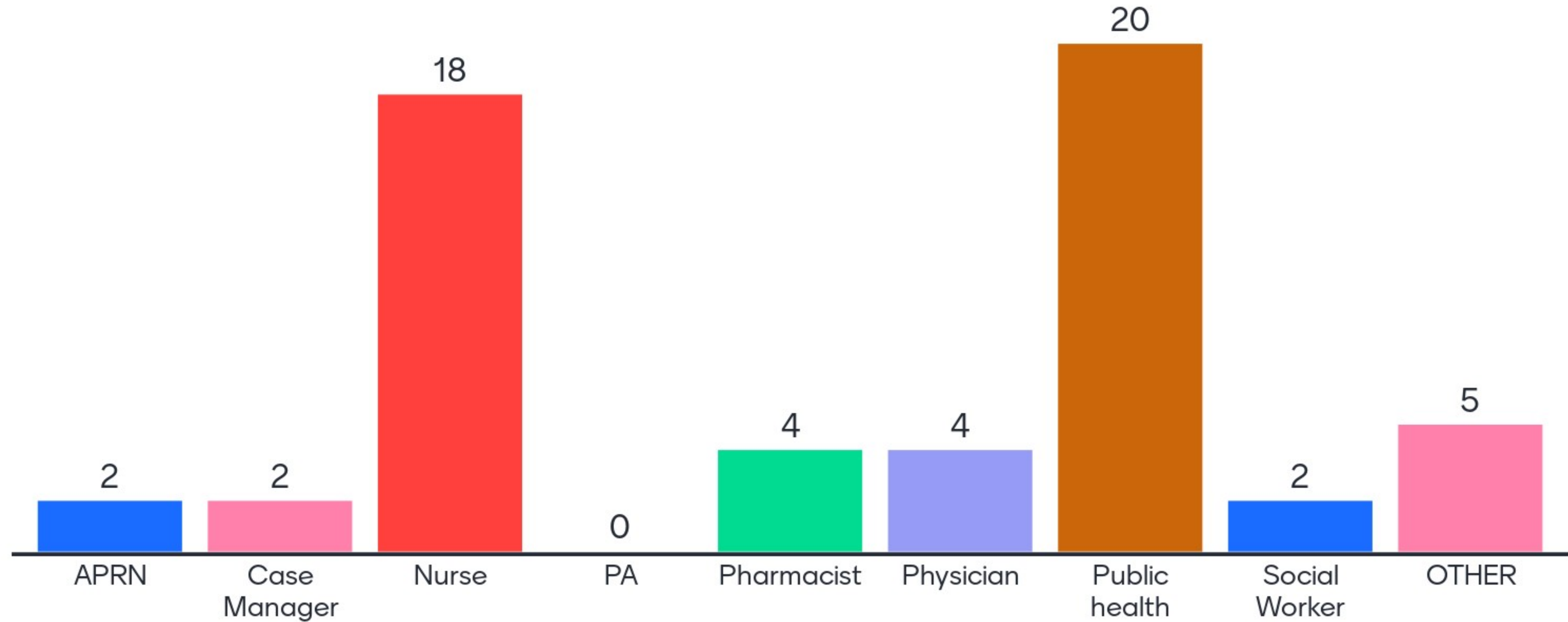
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Southeast AIDS Education and Training Center (SE AETC)

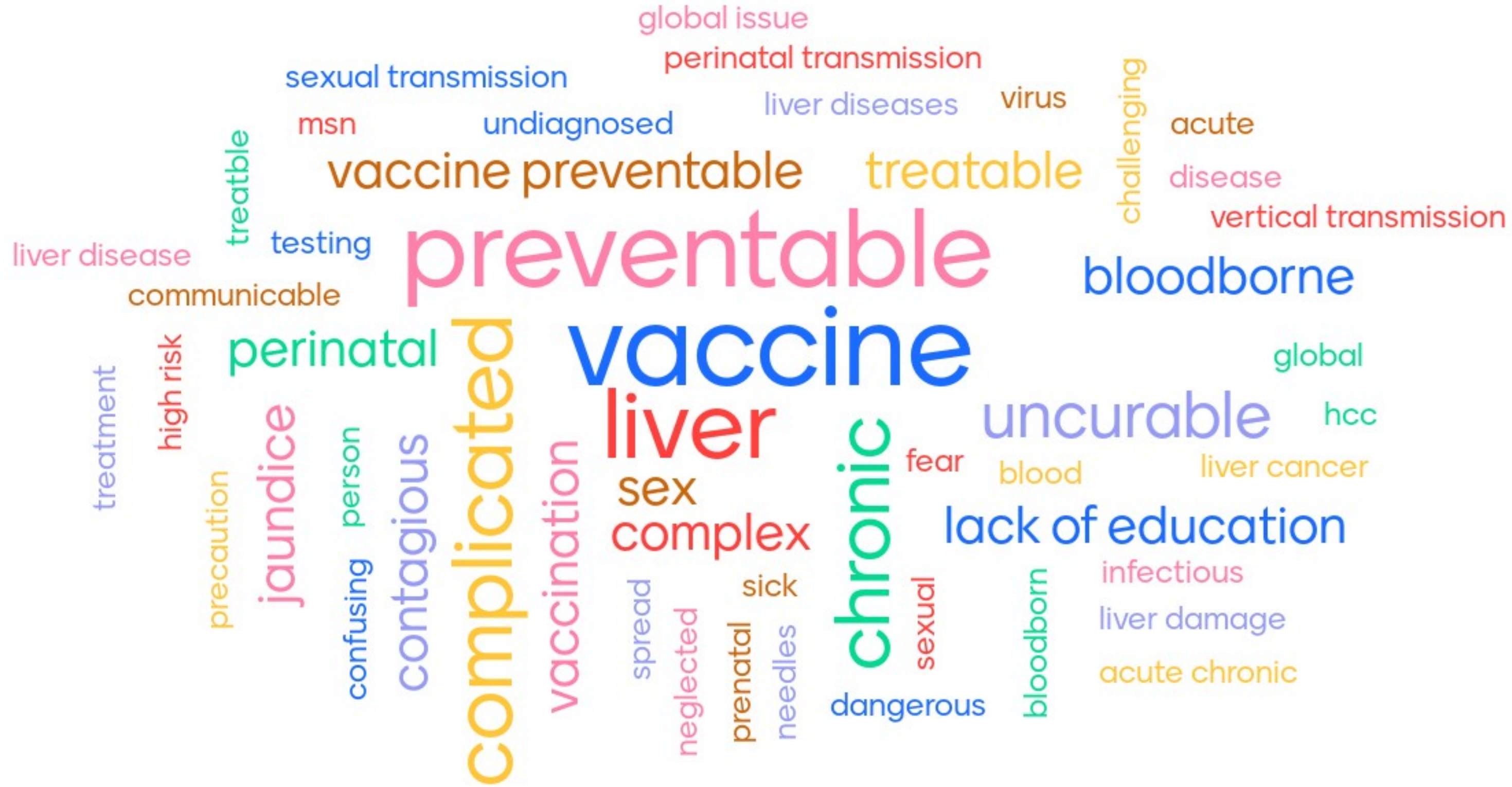


What is your professional role?



What word(s) come to mind when you think of hepatitis B virus (HBV)?

100 responses



Case: Introducing Hep Bee

- 39 y/o engineer from China who has been referred to clinic for a positive HBV test result
- Denies any prior medical history or symptoms related to hepatitis
- Unaware of diagnosis prior to recent testing performed at time of primary care intake
- ALT 50 U/L [upper limit of normal (ULN) per lab 40]
- AST 45 U/L (ULN per lab 40)
- HBV serology reveals:
 - Anti-HBs negative
 - Total Anti-HBc negative
 - HBsAg positive
 - HBeAg negative
 - Anti-HBe positive
- HBV DNA ~4,500 IU/mL



Zooming In: Clinical Questions

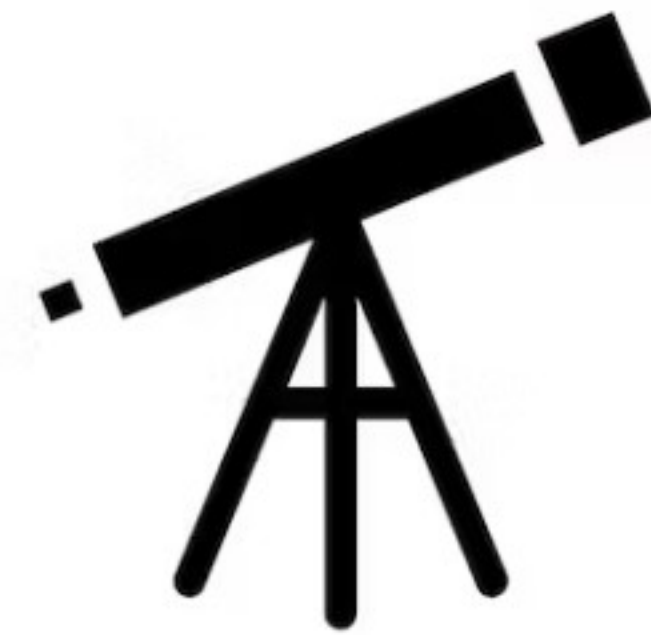


- How do we classify Mr. Bee's HBV infection?
- Should Mr. Bee be treated?
- What treatment options are available for Mr. Bee now and anticipated in the future?



Zooming Out: Points to Ponder

- How impactful is HBV today both globally and domestically?
- Who should be screened and treated for HBV?
- How is treatment for HBV evolving, and how will that impact other aspects of clinical care and scientific investigation?



Goal

- To raise awareness of the state of hepatitis B virus (HBV), evolving screening and treatment recommendations, and future clinical and scholarly opportunities



Objectives

At the end of this grand rounds, you will be able to:

- Describe the evolving epidemiology of HBV globally and in the United States;
- Apply current recommendations for HBV screening, management, and treatment;
- Discuss new HBV treatment and management strategies and their implications for clinical and scholarly interventions.



Take Home Points

1. HBV has a huge health impact on global and domestic populations, who are often at-risk and underserved.
2. Universal HBV screening is now recommended, along with more inclusive HBV vaccination guidelines.
3. Evolving HBV treatment algorithms and new antiviral therapies are transforming clinical care and the opportunities for clinical, research, and scholarly activity.



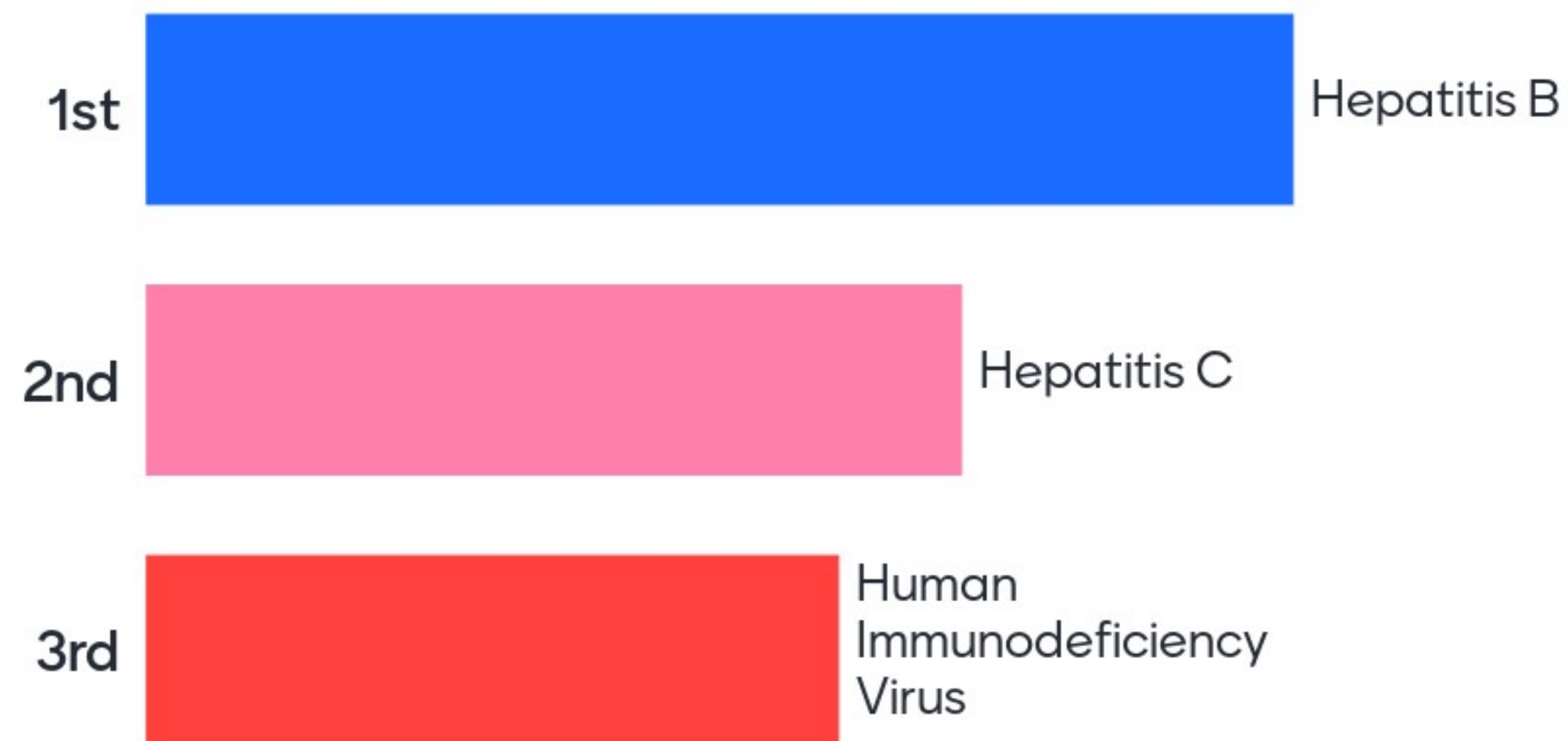
HBV Outline

- Evolving Epidemiology
- Current Management of HBV
- Evolving Approaches to Management and Treatment

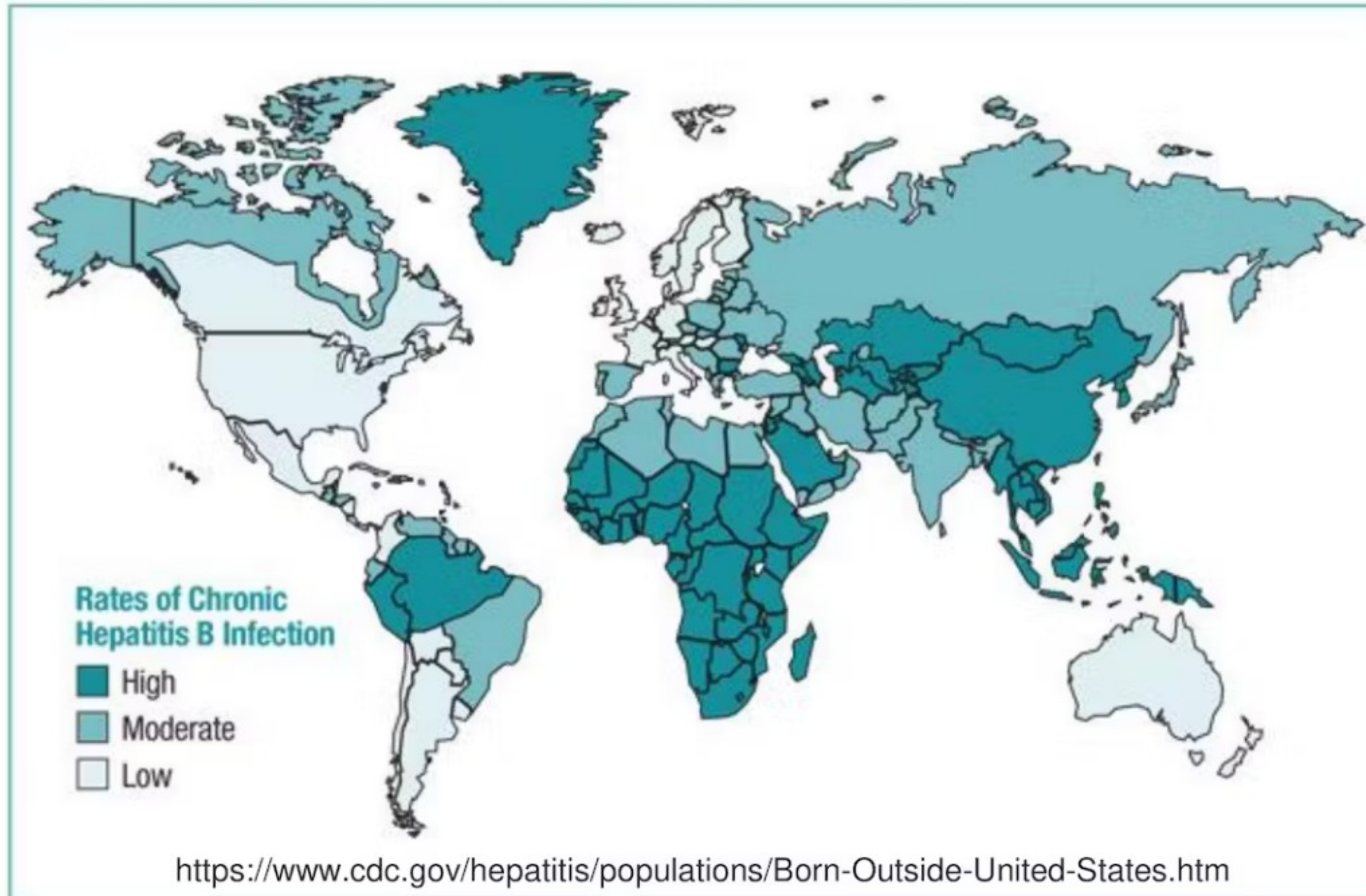
HBV Outline

- **Evolving Epidemiology**
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Rank these chronic viral infections based on the number of deaths attributed globally each year? (1st = Most, 3rd = Least)



Worldwide Rates of Chronic Hepatitis B



As of 2019 per WHO:

~296 million chronic HBV infections worldwide

~1.5 million new infections each year

~820,000 deaths worldwide each year



(In comparison, HCV caused ~290,000 deaths in 2019 while HIV caused ~690,000 deaths in 2022)



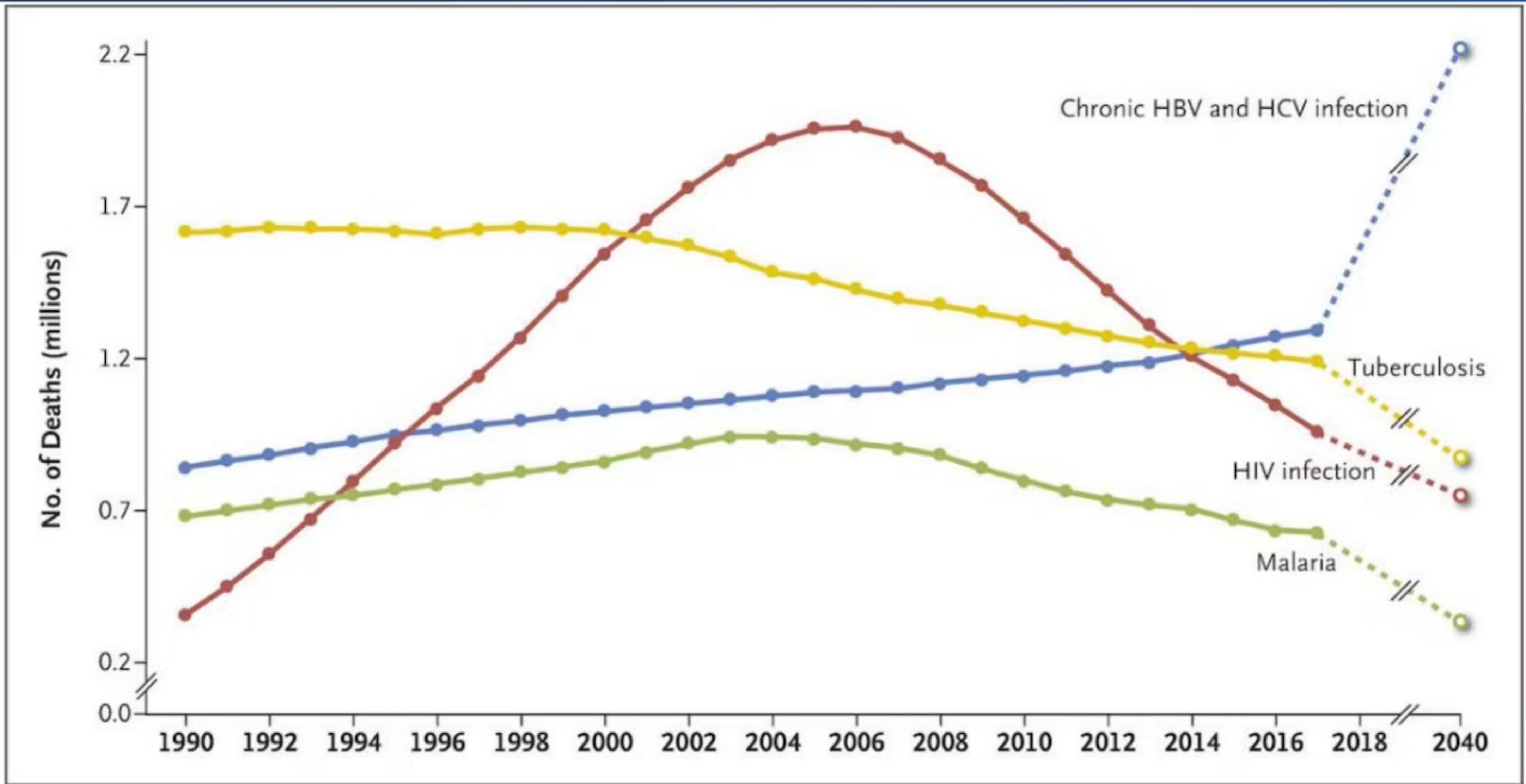


Figure 12 - Worldwide Deaths and Projected Deaths from Chronic Viral Hepatitis as Compared with Deaths from Tuberculosis, Human Immunodeficiency Virus (HIV) Infec



So, why don't we talk about this more?

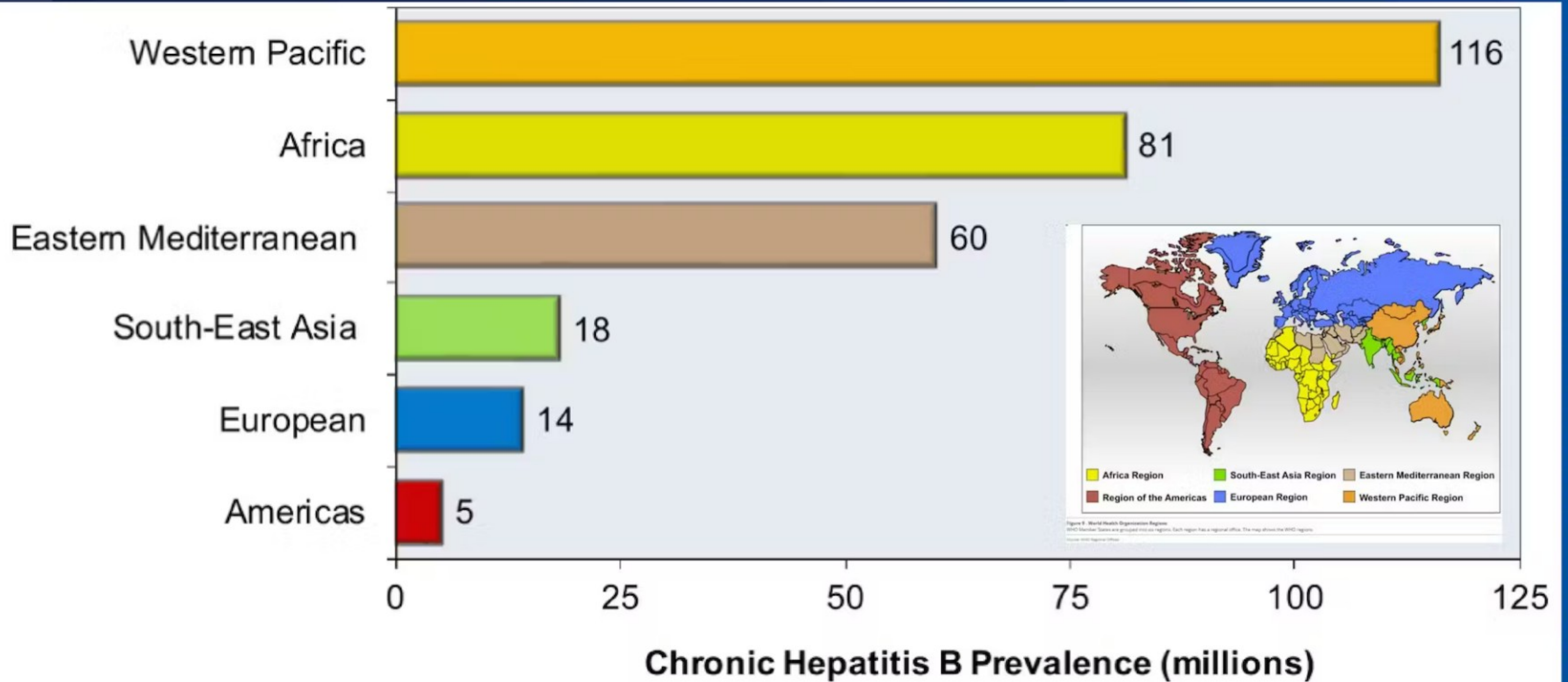
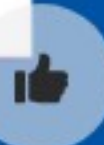


Figure 10 - Chronic Hepatitis B Virus: Global Prevalence Estimates, by World Health Organization Regions, 2019

Source: World Health Organization. Hepatitis B: Key Facts. Geneva: World Health Organization; June 24, 2022.



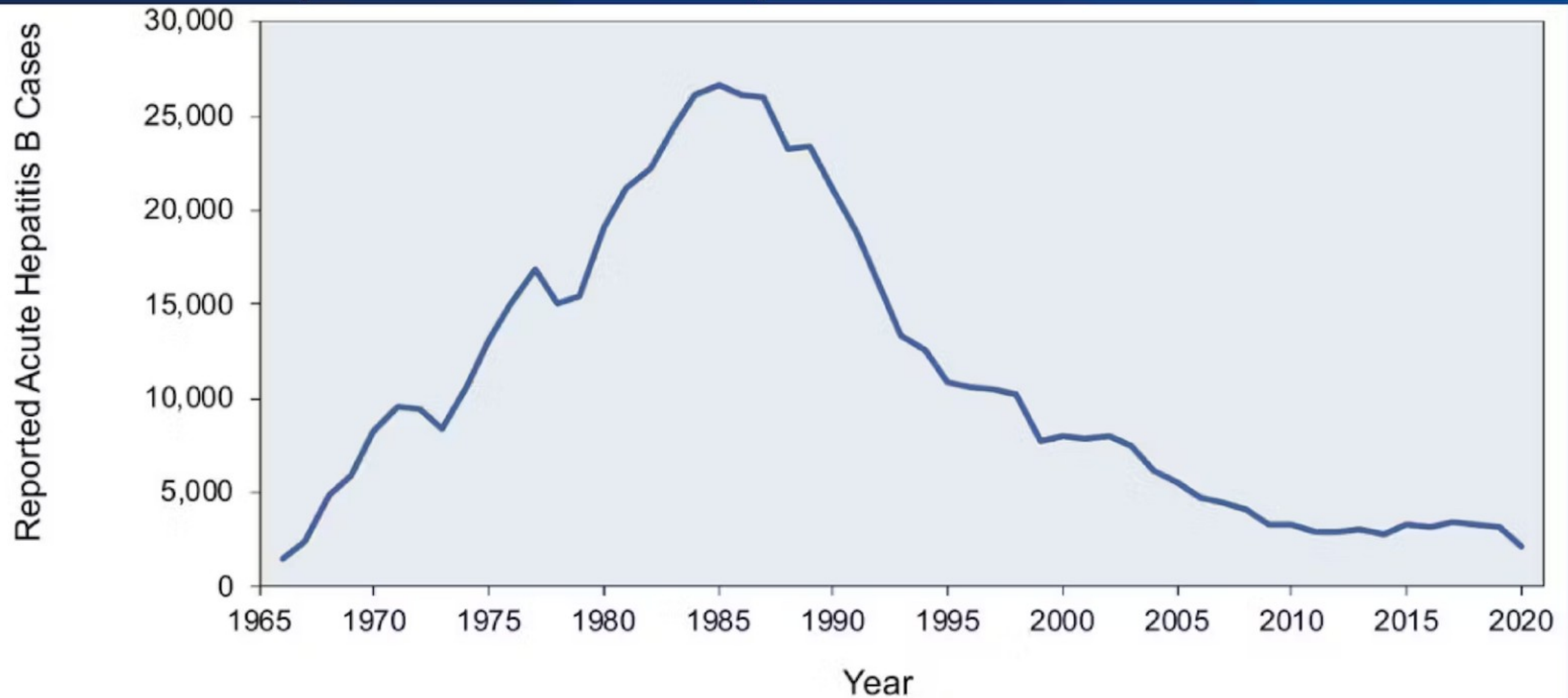


Figure 1 - Acute Hepatitis B Virus: Number of Reported Cases, United States, 1966–2020

Source: Centers for Disease Control and Prevention (CDC). 2020 Viral Hepatitis Surveillance Report—Hepatitis B. Published September 2022.



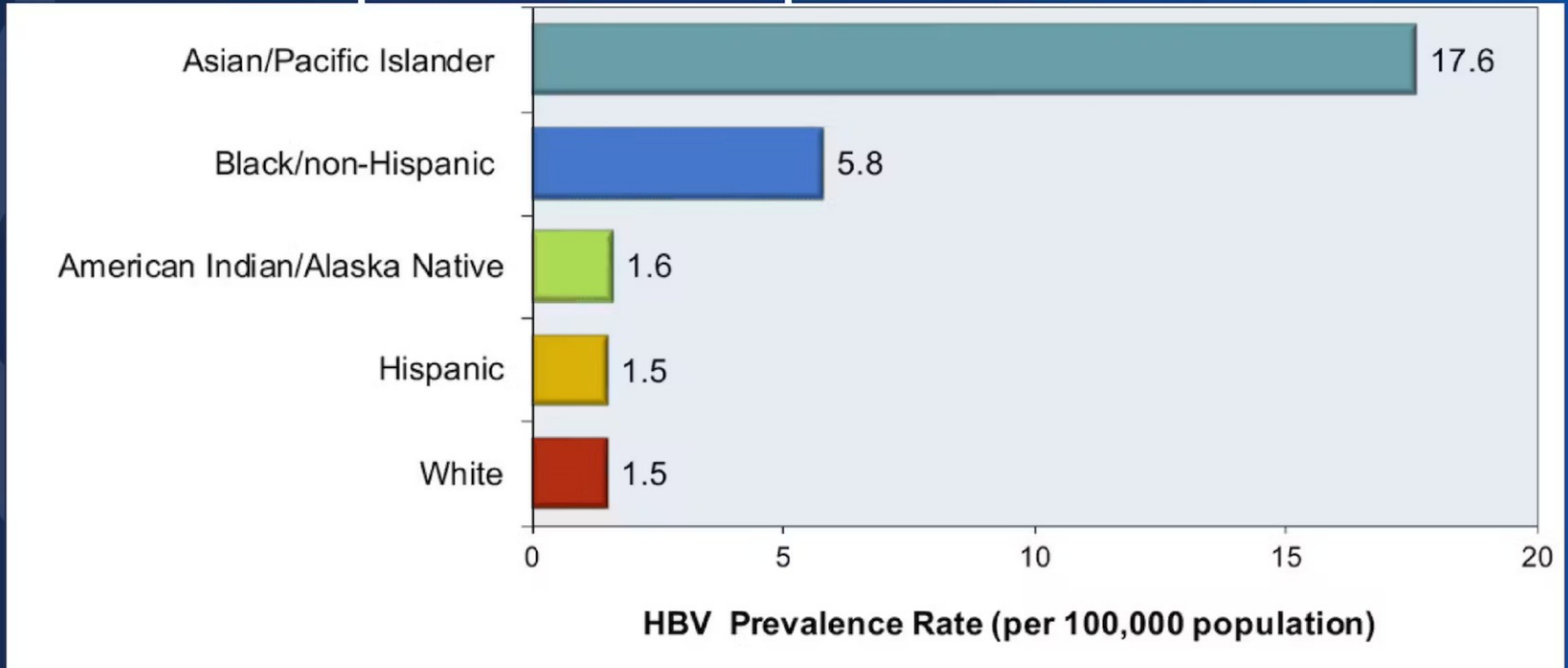
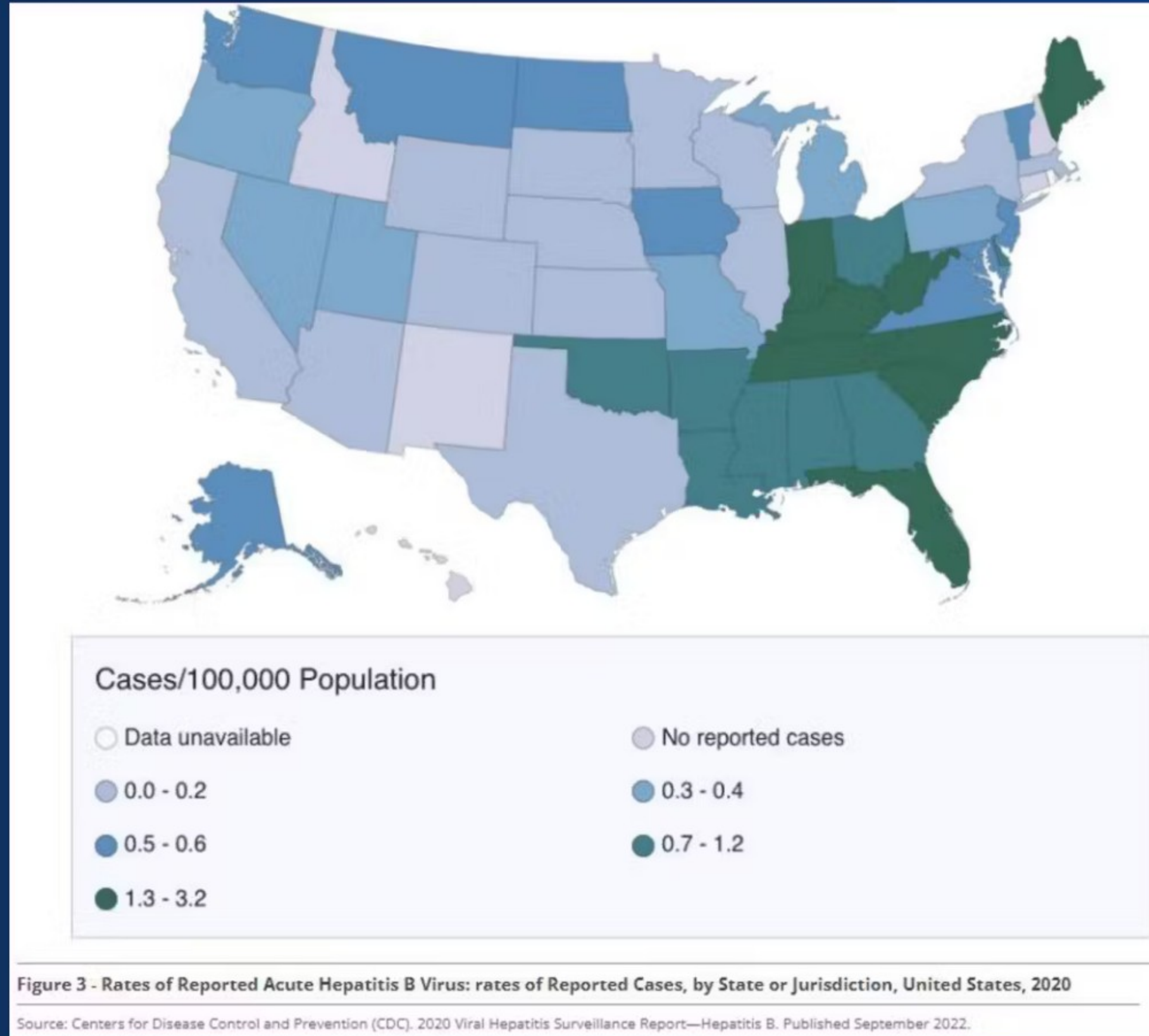


Figure 8 - Hepatitis B Virus Prevalence Rates, by Race/Ethnicity, United States, 2020

Source: Centers for Disease Control and Prevention (CDC). 2020 Viral Hepatitis Surveillance Report—Hepatitis B. Published September 2022.

US prevalence estimates range from ~850,000 to ~2,200,000 (predominantly foreign-born)





Take Home Points

- 1. HBV has a huge health impact on global and domestic populations, who are often at-risk and underserved.**
- 2. Universal HBV screening is now recommended, along with more inclusive HBV vaccination guidelines.**
- 3. Evolving HBV treatment algorithms and new antiviral therapies are transforming clinical care and the opportunities for clinical, research, and scholarly activity.**



How can we better identify people with HBV?

Groups at Increased Risk for HBV (CDC)

- Persons currently or formerly incarcerated in jail, prison, or another detention setting
- Persons with current or past sexually transmitted infections (STIs) or multiple sex partners
- Persons with current or past hepatitis C virus (HCV) infection
- Persons born in regions with an HBV prevalence equal to or greater than 2%
- US-born persons who were not vaccinated as infants and whose parents were born in a region of high HBV prevalence (equal to or greater than 8%)
- Persons with HIV infection
- Persons with current or past injection drug use
- Men who have sex with men
- Infants born to people who are HBsAg-positive
- Household contact with a person who has HBV infection
- Needle-sharing or sexual contacts of persons with known HBV infection
- Patients receiving predialysis, hemodialysis, peritoneal dialysis, or home dialysis
- Persons with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels of unclear etiology
- Persons who request HBV testing due to the potential reluctance to disclose stigmatizing risk factors

Risk Behaviors/Exposures	Risk identified*	No risk identified	Risk data missing
Injection drug use	402	713	1,042
Multiple sexual partners	124	512	1,521
Surgery	91	688	1,378
Sexual contact [§]	46	498	1,613
Needlestick	36	742	1,379
Men who have sex with men [¶]	64	281	952
Household contact (non-sexual) [§]	9	535	1,613
Dialysis patient	31	786	1,340
Occupational	1	970	1,186
Transfusion	1	809	1,347

Figure 11 - Acute Hepatitis B Virus: Reported Risk Behaviors or Exposures, United States, 2020

* Reported confirmed cases.

[†] Reported cases may include more than one risk behavior/exposure. Case reports with at least one of the following risk behaviors/exposures reported 6 weeks to 6 months prior to symptom onset or documented seroconversion if asymptomatic: 1) injection drug use; 2) multiple sexual partners; 3) underwent surgery; 4) men who have sex with men; 5) sexual contact with suspected/confirmed hepatitis B case; 6) sustained a percutaneous injury; 7) household contact with suspected/confirmed hepatitis B case; 8) occupational exposure to blood; 9) dialysis; and 10) transfusion.

[§] Cases with more than one type of contact reported were categorized according to a hierarchy: (1) sexual contact; (2) household contact (nonsexual).

[¶] A total of 1,297 acute hepatitis B cases were reported among males in 2020.

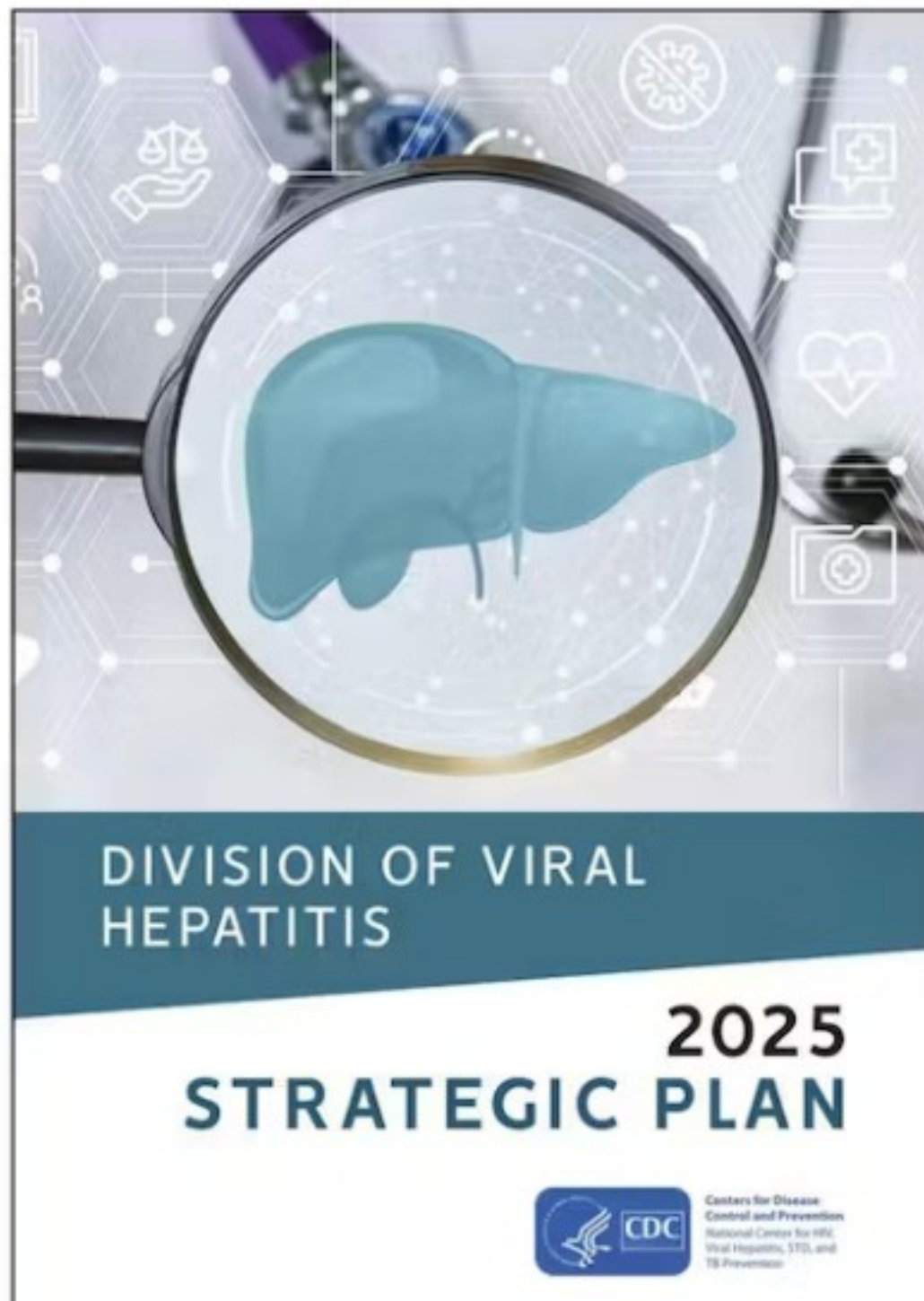


HBV Testing and Diagnosis Cascade

- In the REACH US cohort, only **39.2% tested** for HBV among 53,896 racial and ethnic minority individuals.
- In Kaiser Permanente Hawaii, only **28.3% tested** among 41,263 adults of Asian-Pacific Islander ethnicity
- Of 511,029 commercially insured adults modeled to have HBV:
 - Only **18.6% diagnosed**
 - Of those with **cirrhosis**, only **34.8% treated**
 - Of those with **HCC**, only **48.6% treated**



CDC Department of Viral Hepatitis Strategic Plan 2025



CDC Goals	Baseline	~2025 Target	~2030 Target
New HBV infections	22,200	≤18,000	≤2200
Awareness of HBV infection	32%	≥50%	≥90%
Engagement in HBV care	26%	≥40%	≥80%
HBV-related deaths/100,000 persons	0.46	≤0.37	≤0.16



Rationale For Universal One-Time Adult HBV Screening

- Reduce stigma
- Simplify screening/testing
- Timely diagnosis
- Facilitate linkage to care
- Align testing with vaccination
- Cost-effective

CDC Screening Recommendations for HBV (2023)

(<https://www.cdc.gov/hepatitis/hbv/testingchronic.htm>)

Summary of 2023 HBV screening and testing recommendations

Screen all adults aged 18 years and older at least once in their lifetime using a triple panel test

Screen pregnant people for hepatitis B surface antigen (HBsAg) during each pregnancy regardless of vaccination status and history of testing

Expand periodic risk-based testing to include people incarcerated, people with a history of sexually transmitted infections or multiple sex partners, and people with hepatitis C virus infection

Test anyone who requests HBV testing regardless of disclosure of risk

Update: All adults should be tested at least once for hepatitis B. Have you been tested?

- Hepatitis B infection can cause liver cancer and early death
- Most people with the virus don't know they have it
- Treatment is available — schedule your screening today



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MARCH 10, 2023

ACIP HBV Vaccination Recommendations 2022

- Infants
- Children age 18 years and younger
- Adults age 19 to 59 years
- Adults age 60 years and older with risk factors for HBV

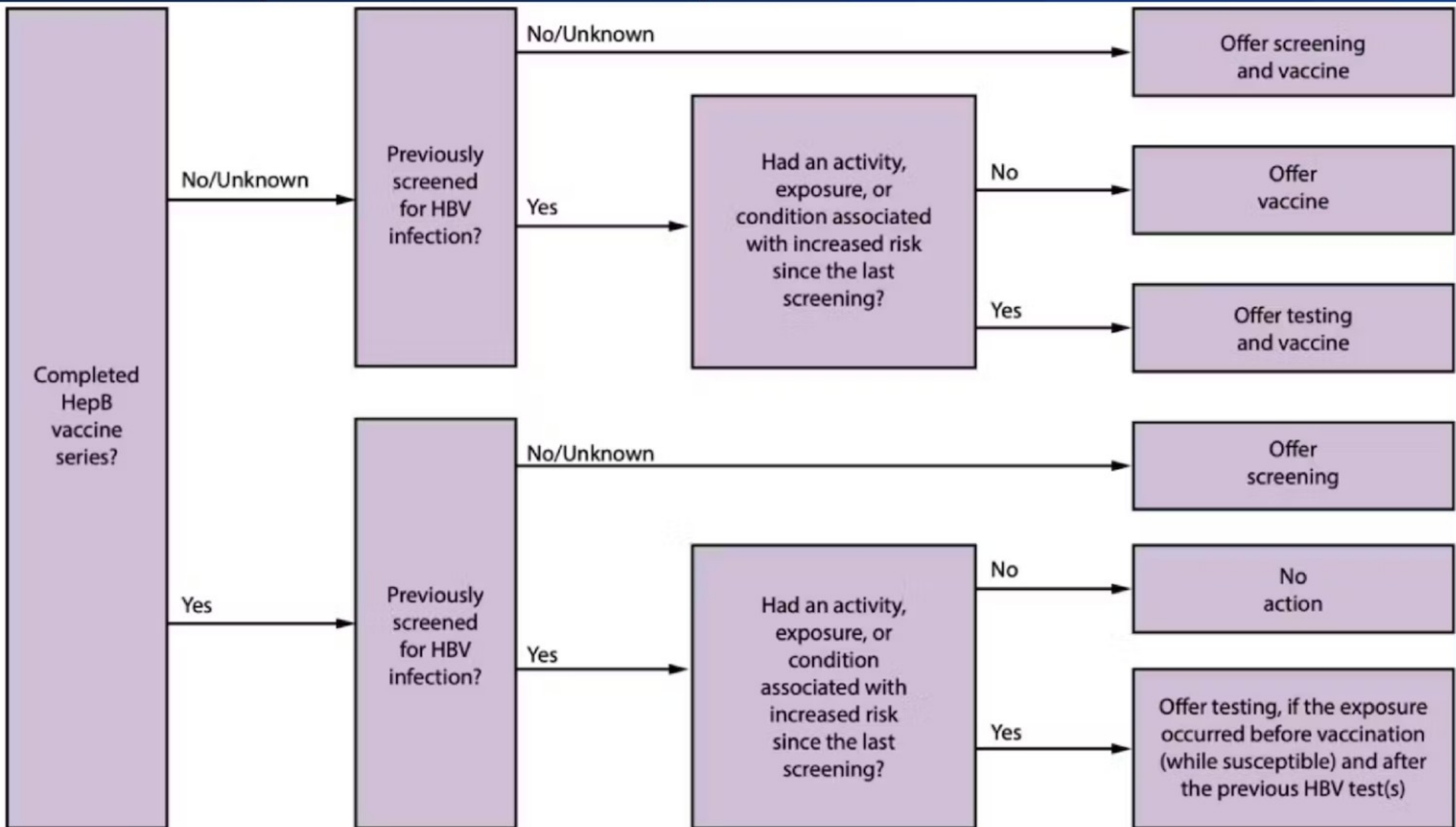


Figure 1 - Incorporating HBV Screening and Testing into a Clinic Workflow: Nonpregnant Adults Aged ≥18 Years without a Known History of HBV Infection



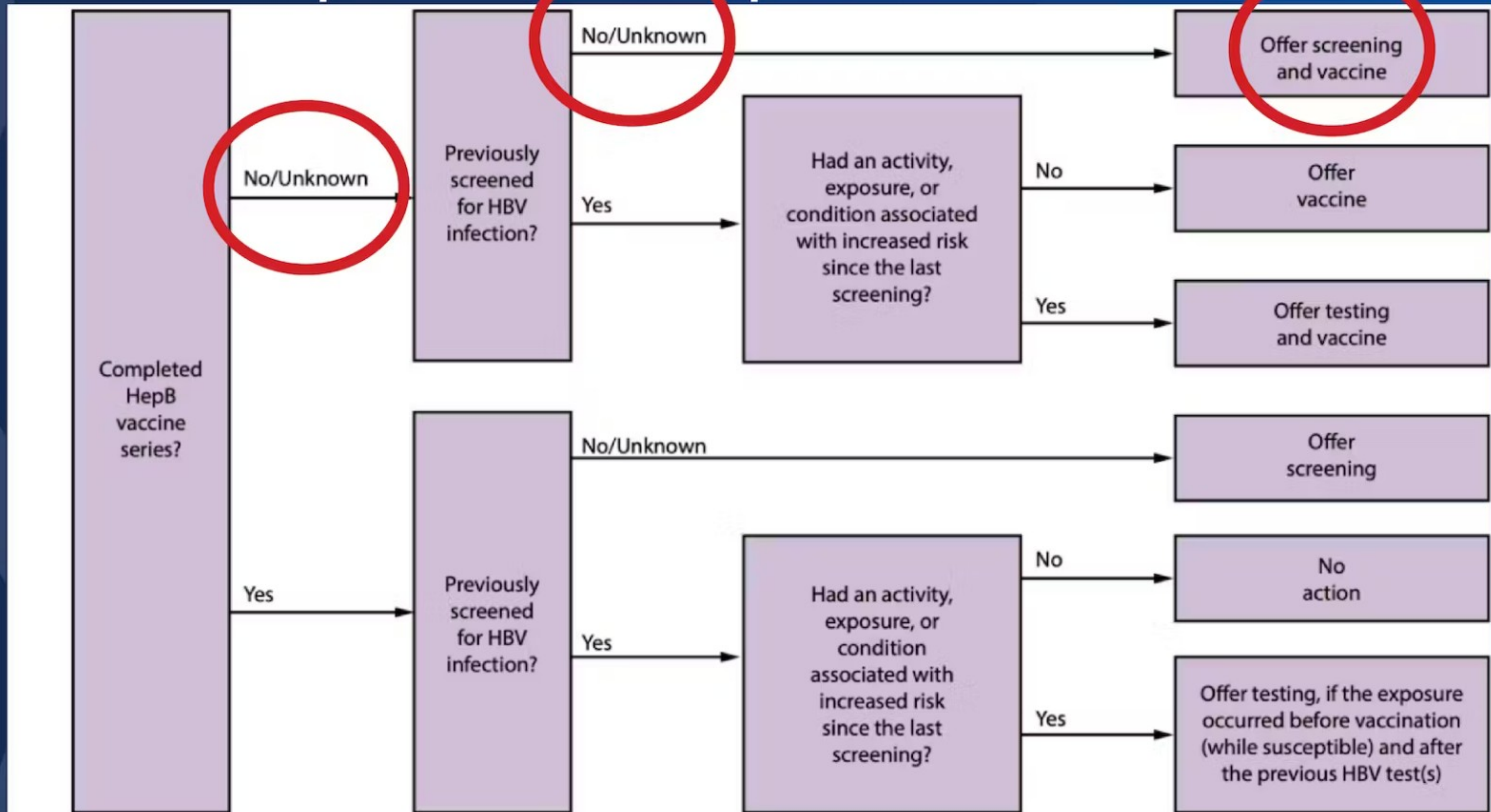


Figure 1 - Incorporating HBV Screening and Testing into a Clinic Workflow: Nonpregnant Adults Aged ≥18 Years without a Known History of HBV Infection

Source: Connors EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72:1-25.

Take Home Points

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2. **Universal HBV screening is now recommended, along with more inclusive HBV vaccination guidelines.**
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HBV Outline

- Evolving Epidemiology
- **Current Management of HBV**
- Evolving Approaches to Management and Treatment

Case: Treating Hep Bee

- 39 y/o engineer from China who has been referred to clinic for a positive HBV test result
- Denies any prior medical history or symptoms related to hepatitis
- Unaware of diagnosis prior to recent testing performed at time of primary care intake
- ALT 50 U/L [upper limit of normal (ULN) per lab 40]
- AST 45 U/L (ULN per lab 40)
- HBV serology reveals:
 - Anti-HBs negative
 - Total Anti-HBc negative
 - HBsAg positive
 - HBeAg negative
 - Anti-HBe positive
- HBV DNA ~4,500 IU/mL



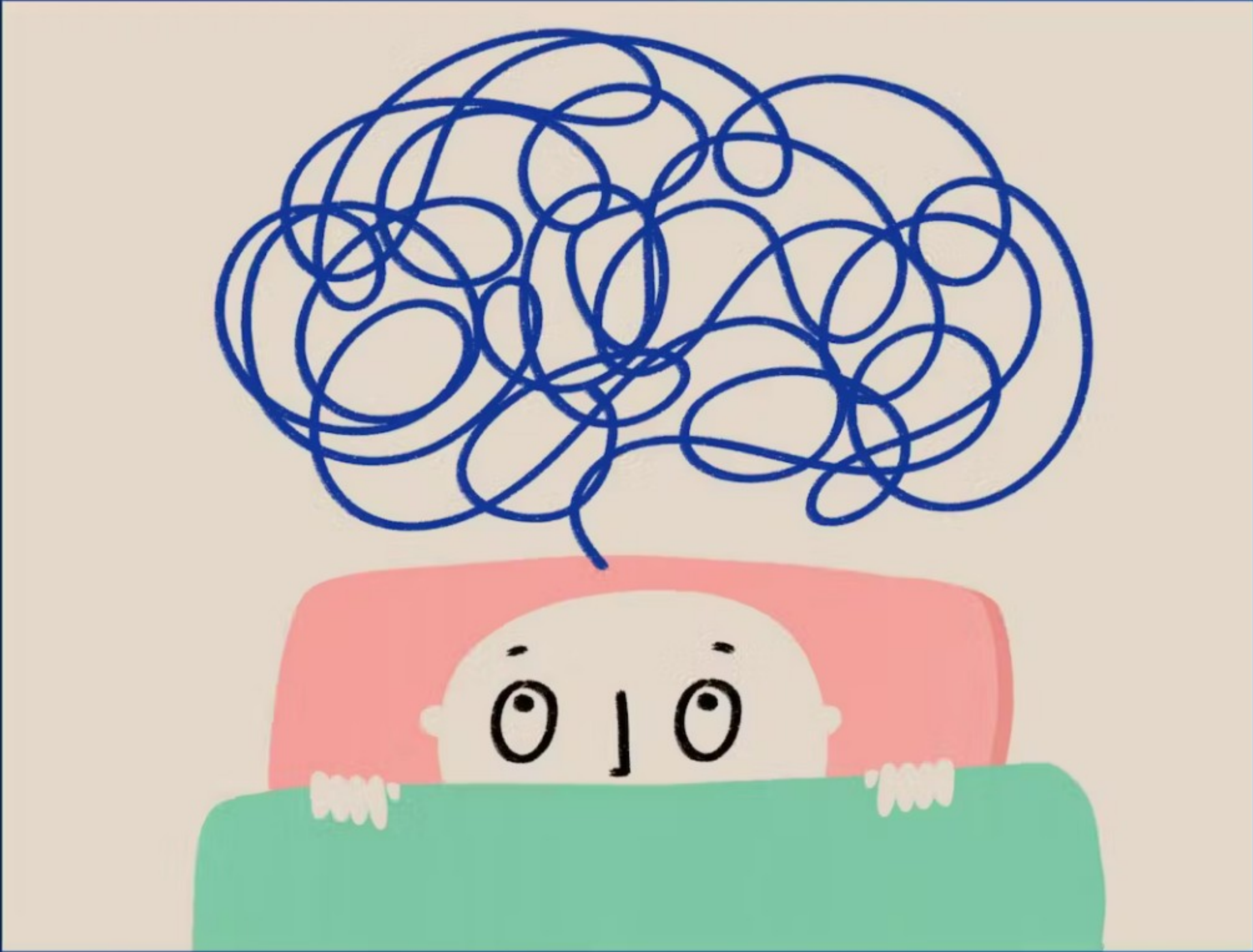
How would you manage Mr. Bee?

Monitor



Treat





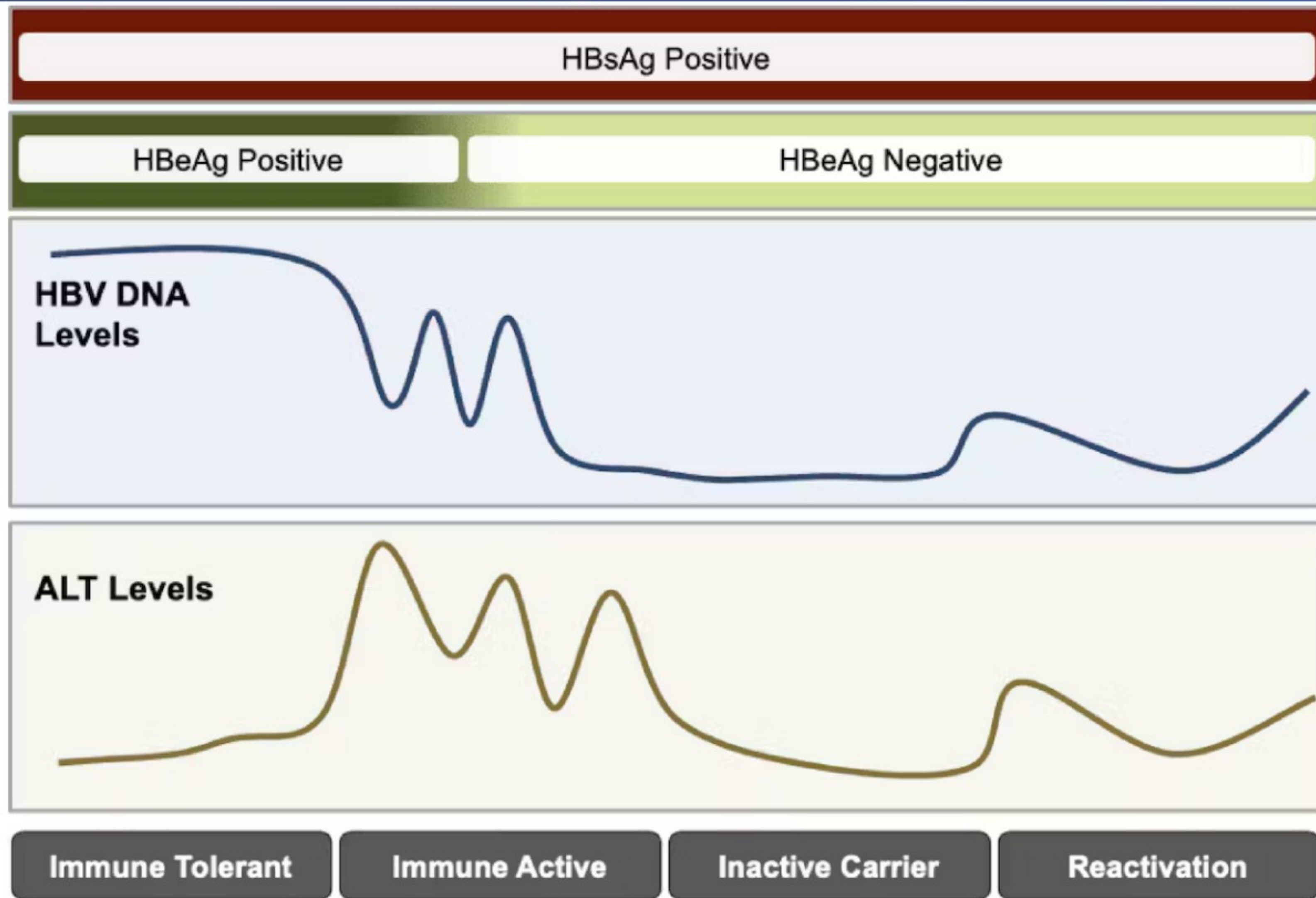


Figure 3 - Hepatitis B Disease Phases

This illustration shows the relationship of different hepatitis B immune phases and fluctuations in HBV DNA and serum alanine aminotransferase (ALT) levels.

Illustration: David H. Spach, MD



Table 1. Phases of Hepatitis B Virus (HBV) Infection, Nomenclature, and Biomarkers.*

Variable	Phase					
	HBeAg-Positive Chronic HBV Infection	HBeAg-Positive Chronic Hepatitis B	HBeAg-Negative Chronic HBV Infection	HBeAg-Negative Chronic Hepatitis B	“Gray Zone”	Occult Hepatitis B
Other phase names	Immune tolerant	Immune (re)active	Inactive carrier state	HBeAg-negative disease	Indeterminate	None
Serologic testing						
HBsAg	Positive	Positive	Positive	Positive	Positive	Negative
Quantitative HBsAg (log ₁₀ IU/ml) [†]	3.5–4.5	3.5–4.5	2.5–3.5	2–3	2–3	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative	Negative
HBe antibodies	Negative	Negative	Positive	Positive	Positive	May be positive
HBV DNA (IU/ml)	Typically >10 ⁷	Typically >10 ⁵ to 10 ⁷	<10 ³	Typically >10 ³ to ≤10 ⁵	2 × 10 ³ (3.3 log ₁₀) to 2 × 10 ⁴ (4.3 log ₁₀)	Low, at detection limit
Alanine aminotransferase	Near ULN	Elevated	Near ULN	Elevated	Fluctuates near ULN	Near ULN
Histologic features on liver biopsy	Minimal necroinflammation or fibrosis	Moderate-to-severe necroinflammation and varying degrees of fibrosis	Minimal necroinflammation and fibrosis	Moderate-to-severe necroinflammation or fibrosis	Minimal or low necroinflammation	Usually minimal or low necroinflammation; fibrosis can be present
cccDNA (assumed copy no./cell) [‡]	Relatively high	Relatively high	Relatively low, or transcriptional activity	Relatively low, or transcriptional activity	Relatively low, or transcriptional activity	Data uncertain
Integrated HBV DNA [§]	Present	Present	Present and accounts for majority of HBsAg	Present and accounts for majority of HBsAg	Present	Present
HBcrAg level	High	High	Low or undetected	Lower than HBeAg-positive states	May be detected	Data not available
HBV RNA level	High	High	Low or undetected	Lower than HBeAg-positive states	May be detected	Data not available

* The abbreviation cccDNA denotes covalently closed circular DNA, HBcrAg HBV core-related antigen, HBeAg hepatitis B e antigen, HBsAg hepatitis B surface antigen, and ULN upper limit of the normal range.

[†] Quantitative HBsAg levels are derived from baseline data in clinical trials of small interfering RNA. Ranges can vary significantly in HBeAg-negative patients, depending on the HBV genotype and HBsAg expression.

[‡] The low number of infected cells in some HBeAg-negative patients, the low cccDNA copy number (1 to 10 per infected cell), and the lack of standards for quantitation allow only a qualitative assumption of cccDNA copy number.

[§] The presence of integrated HBV DNA is usually assumed.



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Alanine aminotransferase	Near ULN	Elevated	Near ULN	Elevated	Fluctuates near ULN	Near ULN
Histologic features on liver biopsy	Minimal necroinflammation or fibrosis	Moderate-to-severe necroinflammation and varying degrees of fibrosis	Minimal necroinflammation and fibrosis	Moderate-to-severe necroinflammation or fibrosis	Minimal or low necroinflammation	Usually minimal or low necroinflammation; fibrosis can be present
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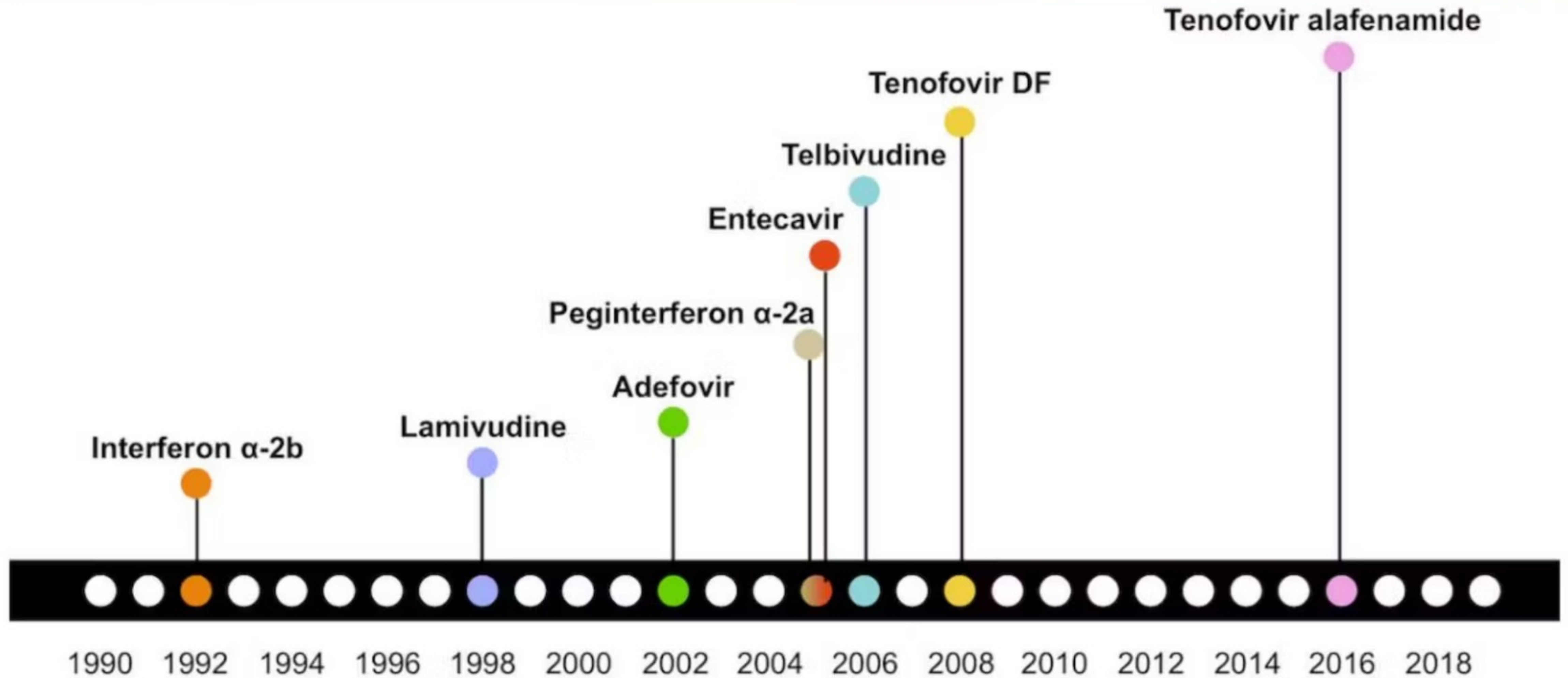
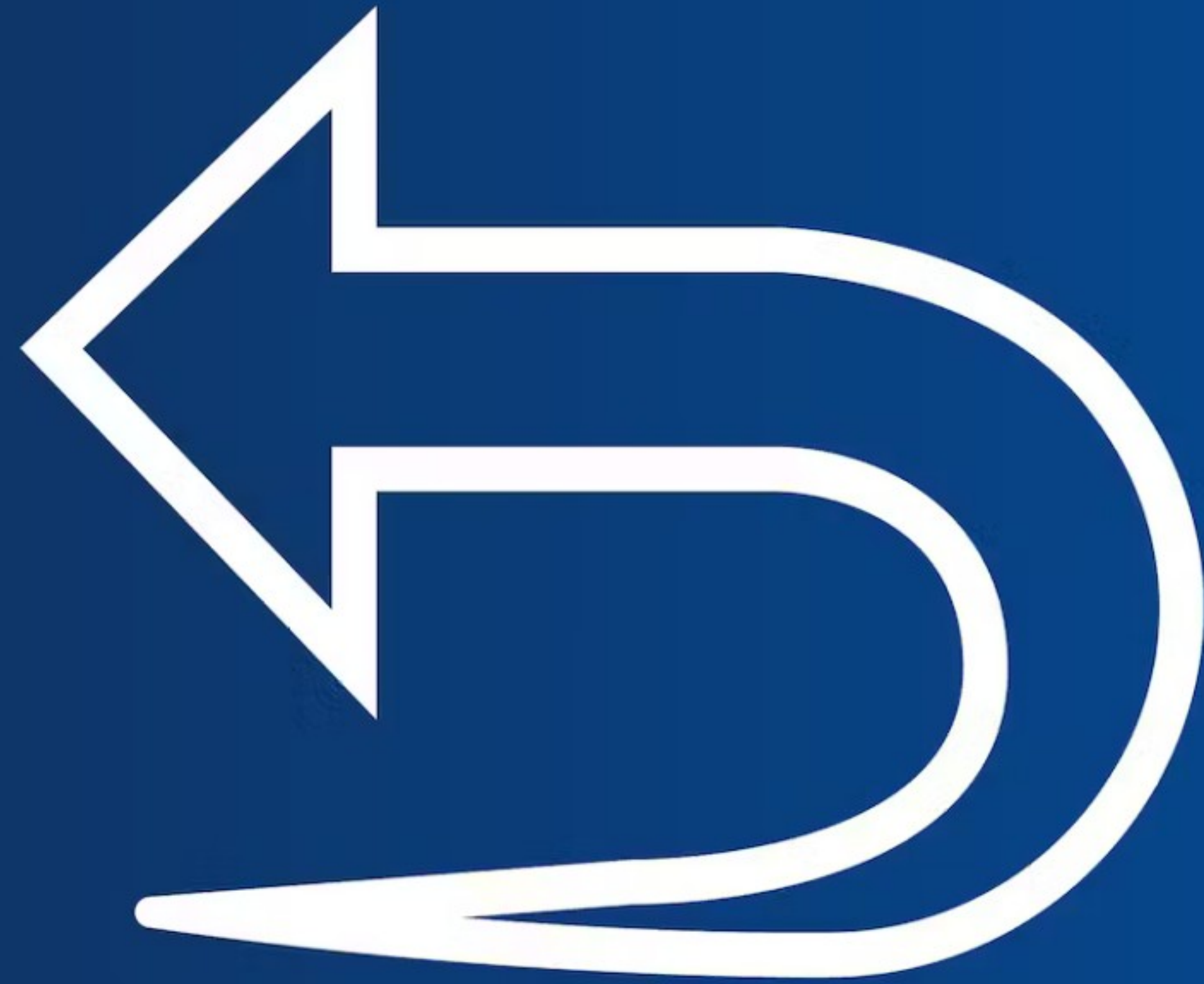


Figure 1 - Agents Approved by the U.S. FDA for the Treatment of Hepatitis B Virus (HBV) Infection
This graphic shows the timeline of FDA approval in the United States for agents used to treat chronic HBV infection.





Hepatitis B Infection or Reactivation After Switch to 2-Drug Antiretroviral Therapy: A Case Series, Literature Review, and Management Discussion

Shilpa Vasishta, MD,^a Douglas Dieterich, MD,^b Michael Mullen, MD,^a and Judith Aberg, MD^a

J Acquir Immune Defic Syndr • Volume 94, Number 2, October 1, 2023

- Four individuals with HBV infection or reactivation after ART switch identified
- Two had HBV susceptibility, 1 had core Ab reactivity, and 1 had surface Ag reactivity preswitch
- Two presented with fulminant hepatitis, with 1 required liver transplantation
- **Takeaway:** Careful patient selection and monitoring needed when considering two-drug antiretroviral therapy for HIV, including assessment of serologies, vaccination and confirmation of immunity, and risk stratification



HBV Treatment Recommendation Based on Major Organization Guidelines			
Indication	AASLD 2018	APASL 2015	EASL 2017
Decompensated Cirrhosis	<ul style="list-style-type: none"> • Treat all¹ and • Refer for liver transplantation 	<ul style="list-style-type: none"> • Treat all¹ 	<ul style="list-style-type: none"> • Treat all¹
Compensated Cirrhosis	<ul style="list-style-type: none"> • Treat all¹ 	<ul style="list-style-type: none"> • Treat if: <ul style="list-style-type: none"> - HBV DNA >2,000 IU/mL or - ALT elevated 	<ul style="list-style-type: none"> • Treat all¹
Without Cirrhosis	<ul style="list-style-type: none"> • Treat if: <ul style="list-style-type: none"> - ALT elevation ($\geq 2x$ ULN²) or - Significant histologic disease⁴ and - HBV DNA >2000 IU/mL if HBeAg-negative - HBV DNA >20,000 IU/mL if HBeAg-positive 	<ul style="list-style-type: none"> • Treat if: <ul style="list-style-type: none"> - ALT elevation ($> 2x$ ULN³) or - Significant histologic disease⁴ and - HBV DNA >2000 IU/mL if HBeAg-negative - HBV DNA >20,000 IU/mL if HBeAg-positive 	<ul style="list-style-type: none"> • Treat if: <ul style="list-style-type: none"> - ALT >40 IU/L, HBV DNA >2000 IU/mL, and biopsy evidence of at least moderate necroinflammation (or at least moderate fibrosis) or - HBV DNA >2000 IU/mL and biopsy evidence of at least moderate fibrosis or - HBV DNA >20,000 IU/mL and ALT > 2x ULN³ regardless of degree of fibrosis

¹ Regardless of HBV DNA, ALT, or HBeAg status; ² Upper limit of normal, defined as ALT 35 for men, 25 for women; ³ Defined as ALT 40 for both men and women; ⁴ Defined as at least moderate necroinflammation or at least moderate fibrosis according to histopathologic grading/staging.

Figure 4 - Guidelines for the Treatment of Chronic Hepatitis B

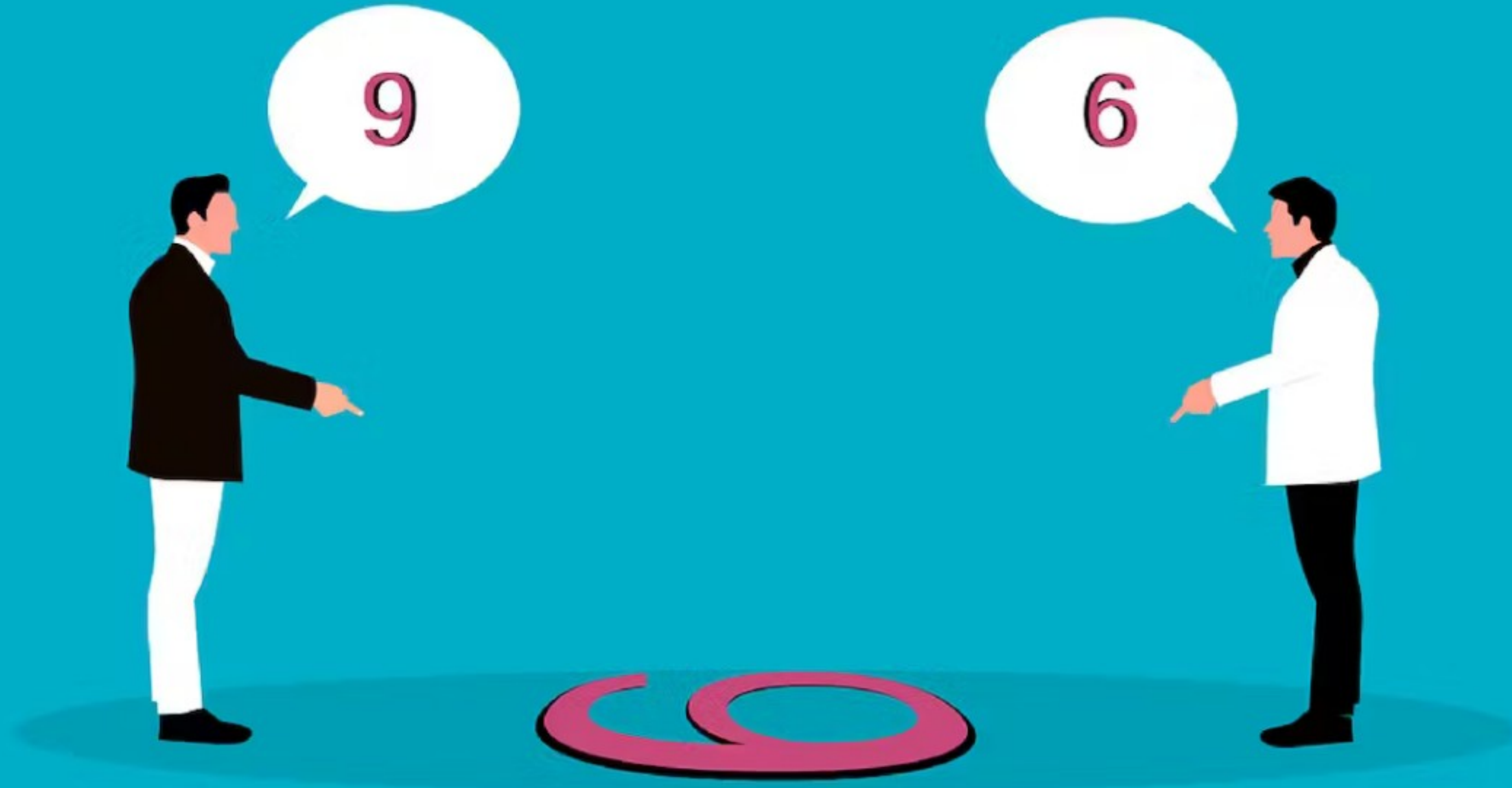
Abbreviations: AASLD = American Association for the Study of Liver Diseases; APASL = Asian Pacific Association for the Study of the Liver; EASL = European Association for the Study of the Liver; ALT = alanine aminotransferase; ULN = upper limit of normal



Adding Insult to Injury... Defining “Normal” ALT

- AASLD and EASL do NOT recommend using reference laboratory cutoffs to define “normal” values.
 - AASLD ULN
 - 35 U/L for Males
 - 25 U/L for Females
 - EASL ULN
 - 40 IU/L for Males and Females
- ALT levels that lower than these limits STILL may not exclude significant liver disease
- Elevated ALT or AST above ULN is associated with increased liver-related mortality





HBV Outline

- Evolving Epidemiology
- Current Management of HBV
- **Evolving Approaches to Management and Treatment**

Reframing the Problem

HIV

~~Immunodeficiency syndrome~~

Viral infection

Hepatitis C Virus

~~Inflammatory liver disease~~

Viral infection

Hepatitis B Virus

~~Inflammatory liver disease~~

Viral infection



Facts About HBV That “Doesn’t Warrant Treatment”

- Increases risk of hepatocellular carcinoma, even in noncirrhotic
- Increases risk of other solid malignancies
- Increases risk of multiple autoimmune conditions
- Increases risk of fulminant liver disease on immunosuppression
- Contribute to stigma and other patient reported outcomes

What If... In a Simpler (HBV Treatment) World?



▪ Age and Viral Load Driven Criteria

- If age <30, treat if HBV DNA >2000 IU/mL and ALT > ULN
- If age ≥30, treat if HBV DNA >2000 IU/mL
- Treat all with HBV with cirrhosis
- Treat all with HBV and HIV

▪ Liver Inflammation Driven Criteria

- If ALT > ULN, treat
- If ALT normal, treat if HBV DNA >2000 IU/mL
- Treat all with HBV with cirrhosis
- Treat all with HBV and HIV

Hepatitis B Management: Guidance for the Primary Care Provider

Last updated February 25, 2020

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 Hepatitis B Primary Care Workgroup, a multidisciplinary panel of national experts in the field of viral hepatitis B, including representation from hepatology, infectious diseases, pharmacy, 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 Hep B Free — Bay Area and Project ECHO™ and did not receive any outside funding.

Collaboration with University of Washington

This guidance was produced in collaboration with the University of Washington’s National Hepatitis Training Center (HTC). The UW HTC will host and feature the most current version of these guidelines on the free *Hepatitis B Online* website ([hepatitisB.uw.edu](https://www.hepatitisB.uw.edu)). The UW HTC is funded by the Centers for Disease Control and Prevention (CDC).

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PUBLIC HEALTH

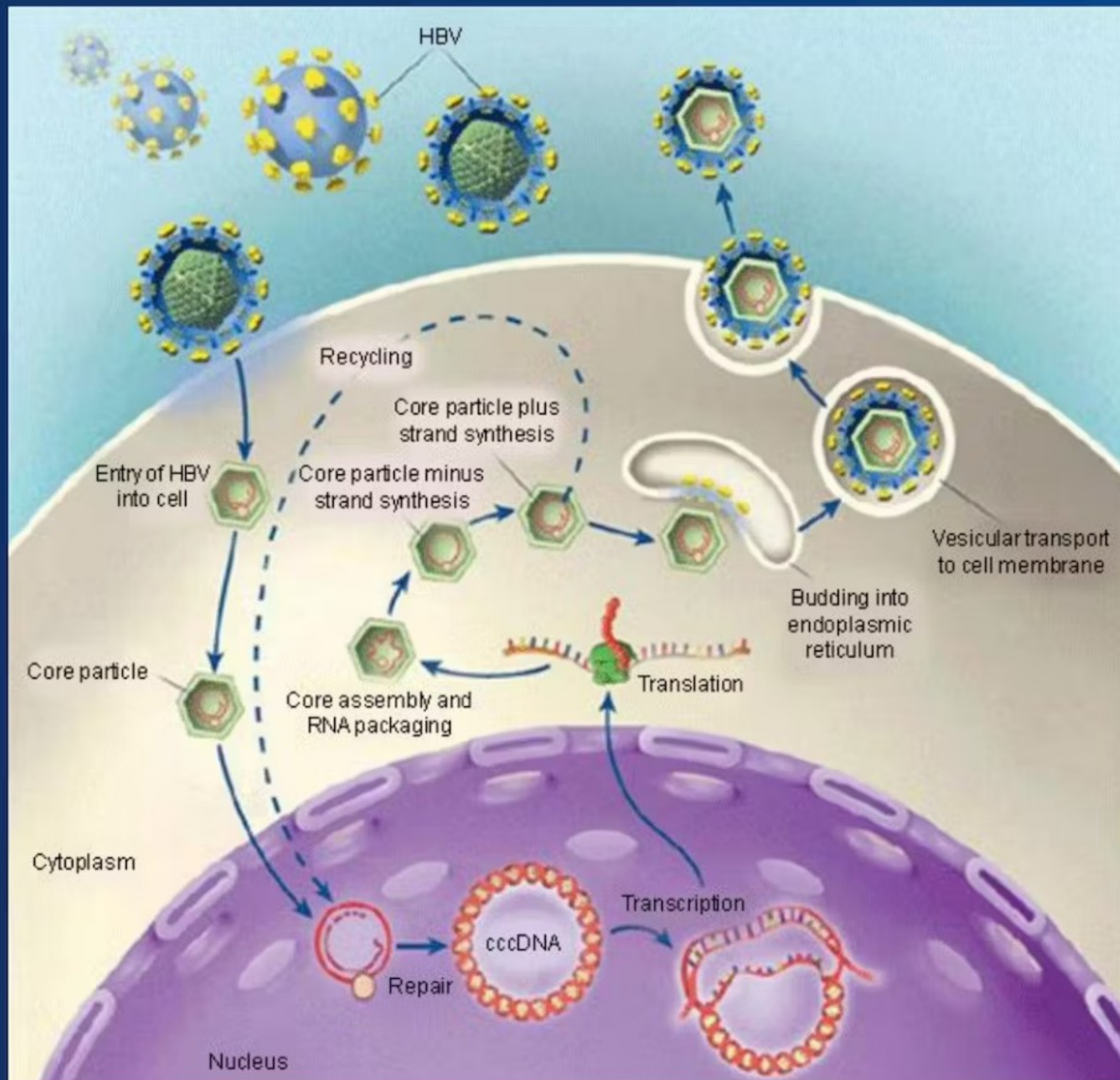
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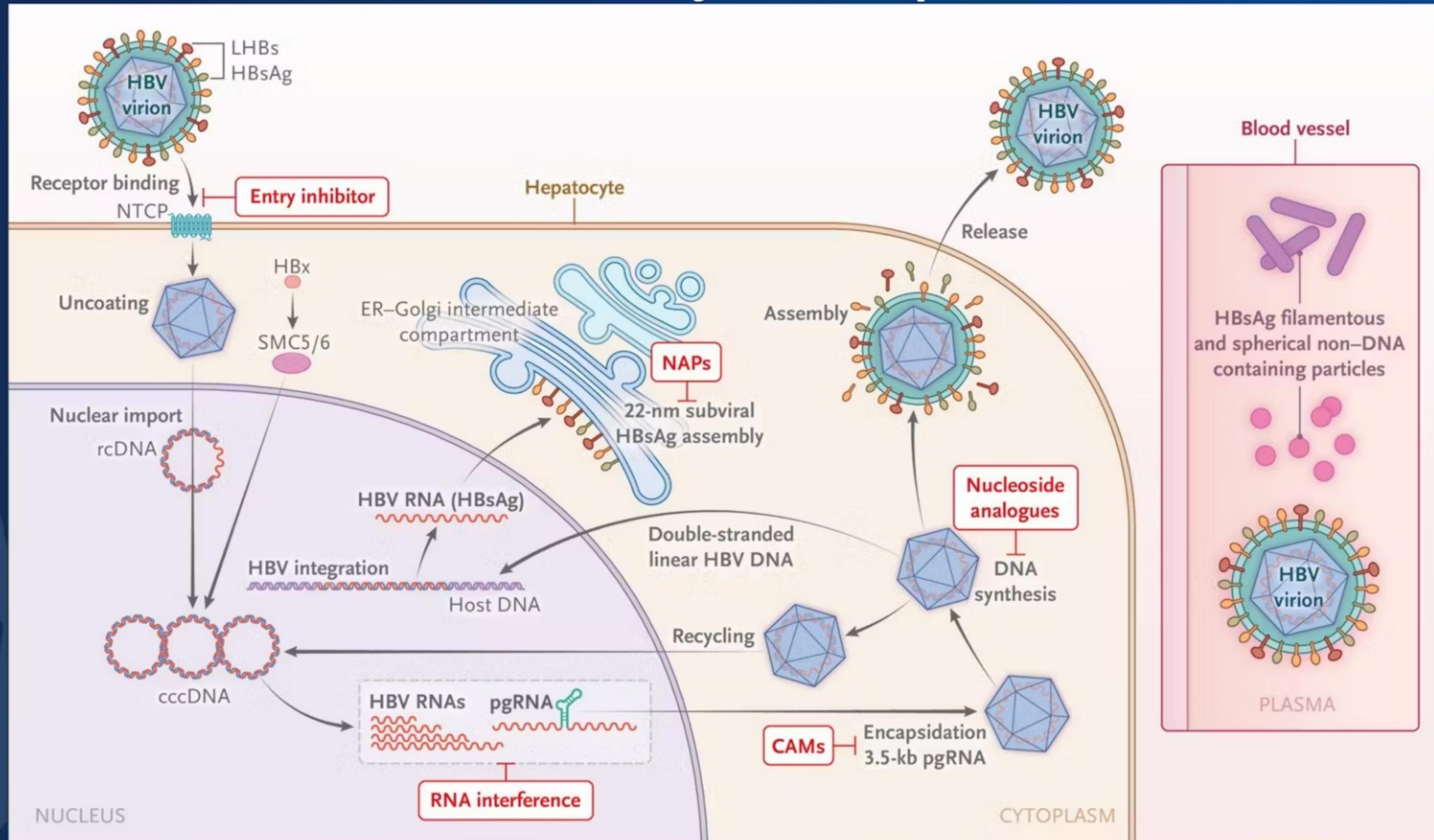
HBV Life Cycle



Ganem D et al. *NEJM* 2004.

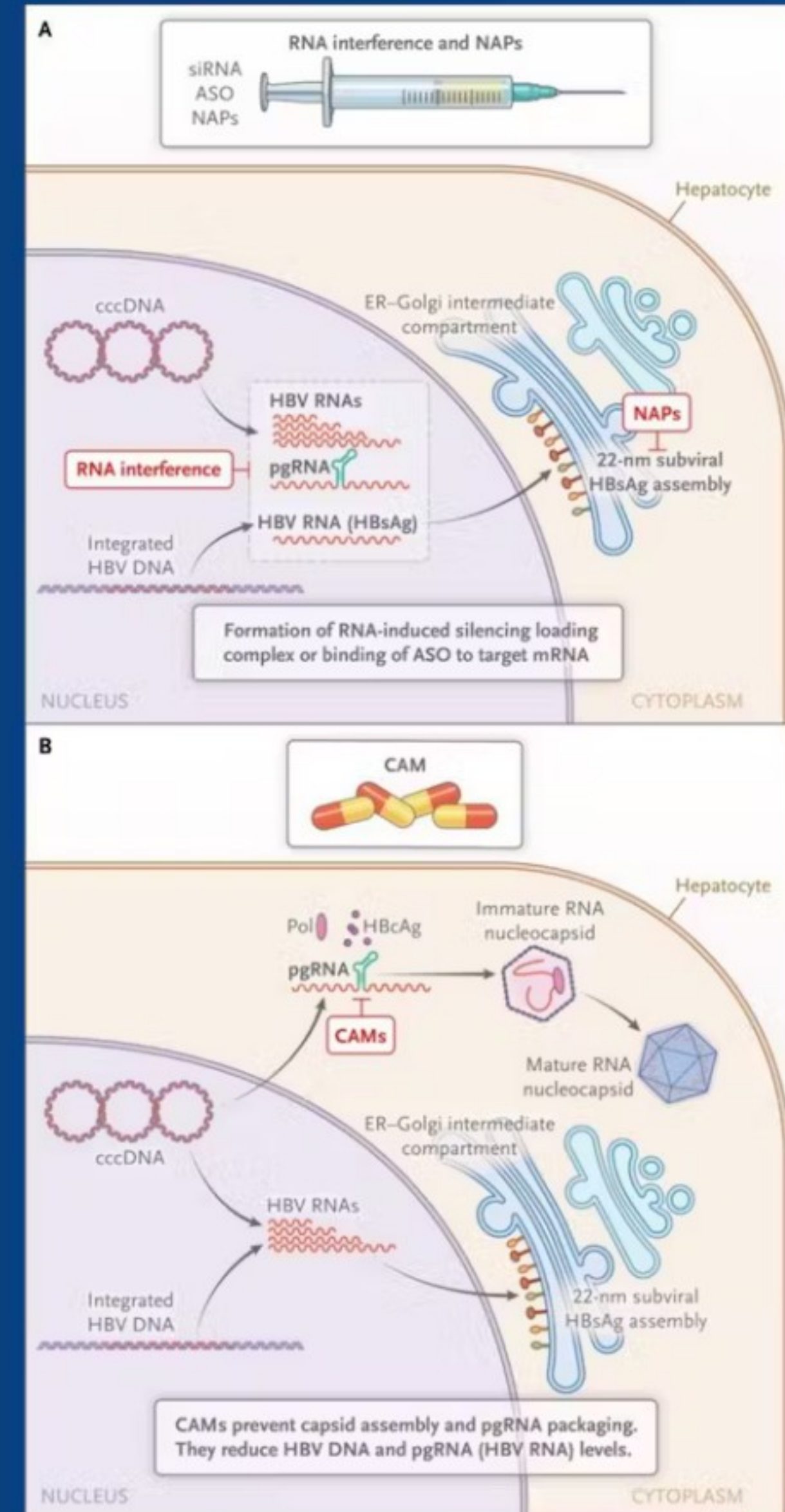
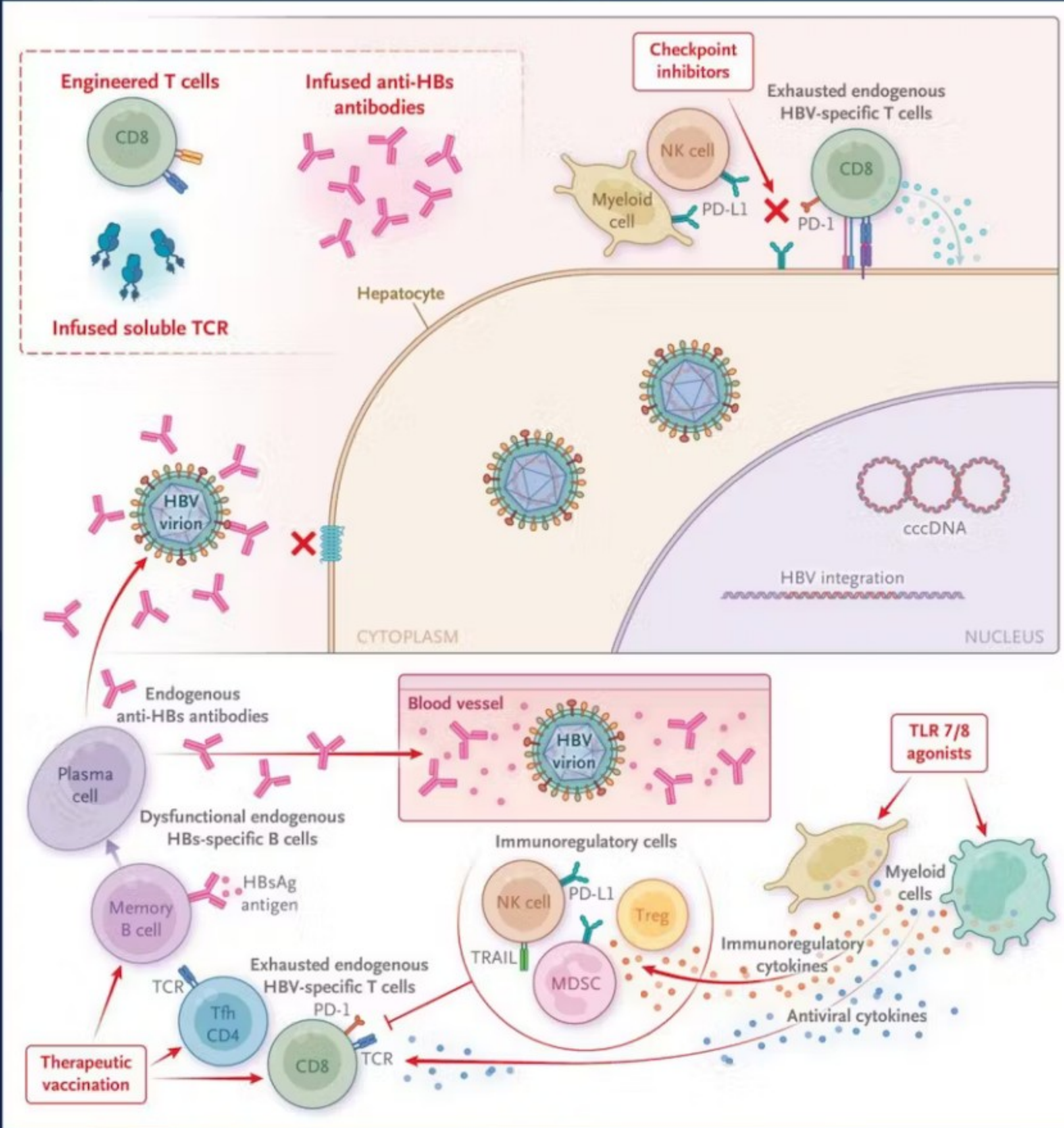


HBV Life Cycle Updated



Potential Molecular and Immunotherapeutic Targets

Mechanisms of Action of RNA Interference Therapeutics, CAMs, and NAPs



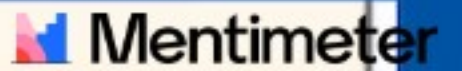
AETC AIDS Education & Training Center Program
Southeast



Table 2. New Anti-HBV Compounds in Clinical Development.

Type and Compound	Originator	Phase*
Capsid assembly modulators		
Vebicorvir (ABI-H0731)	Assembly Biosciences	Phase 2 terminated
ABI-H3733		Phase 1
ABI-4334		Preclinical studies
Morphothiadin (GLS4)	HEC Pharma	Phase 2
JNJ-6379	Janssen	Phase 2b
EDP-514	Enanta	Phase 2
RG7907	Roche	Phase 2
QL-007	Qilu	Phase 1
Canocapavir	Zhimeng Biopharma	Not available
ALG-000184	Aligos Therapeutics	Phase 1
AB-836	Arbutus	Phase 1 and 2
VNRX-9945	Venatorx	Phase 1 terminated
O7049839	Roche	Phase 1

siRNA agents†



RG6346 (RO7445482)	Roche/Dicerna	Phase 2
JNJ-3989	Janssen	Phase 2b
AB7-29-001	Arbutus	Phase 2
VIR-2218	Vir Biotechnology	Phase 2
ALG-125755	Aligos Therapeutics	Phase 1
Antisense oligonucleotides		
Bepirovirsen (GSK3228836)	GSK	Phase 2
RO7062931	Roche	Phase 1
ALG-020572-401	Aligos Therapeutics	Phase 1
Nucleic acid polymers: REP 2139, REP 2165	Replicor	Phase 2
Active-site polymerase inhibitor: ATI-2173	Antios	Phase 2
Entry inhibitor: bulevirtide	Gilead	Phase 3 (hepatitis D)
Transcriptional inhibitor: nitazoxanide	Romark Laboratories/ Lupin	Phase 2

* The information on study status is from ClinicalTrials.gov, accessed December 4, 2022.

† The abbreviation siRNA denotes small interfering RNA.



Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection

M.-F. Yuen, S.-G. Lim, R. Plesniak, K. Tsuji, H.L.A. Janssen, C. Pojoga, A. Gadano, C.P. Popescu, T. Stepanova, T. Asselah, G. Diaconescu, H.J. Yim, J. Heo, E. Janczewska, A. Wong, N. Idriz, M. Imamura, G. Rizzardini, K. Takaguchi, P. Andreone, M. Arbune, J. Hou, S.J. Park, A. Vata, J. Cremer, R. Elston, T. Lukić, G. Quinn, L. Maynard, S. Kendrick, H. Plein, F. Campbell, M. Paff, and D. Theodore, for the B-Clear Study Group*

CONCLUSIONS

In this phase 2b trial, bepirovirsen at a dose of 300 mg per week for 24 weeks resulted in sustained HBsAg and HBV DNA loss in 9 to 10% of participants with chronic HBV infection. Larger and longer trials are required to assess the efficacy and safety of bepirovirsen. (Funded by GSK; B-Clear ClinicalTrials.gov number, NCT04449029.)

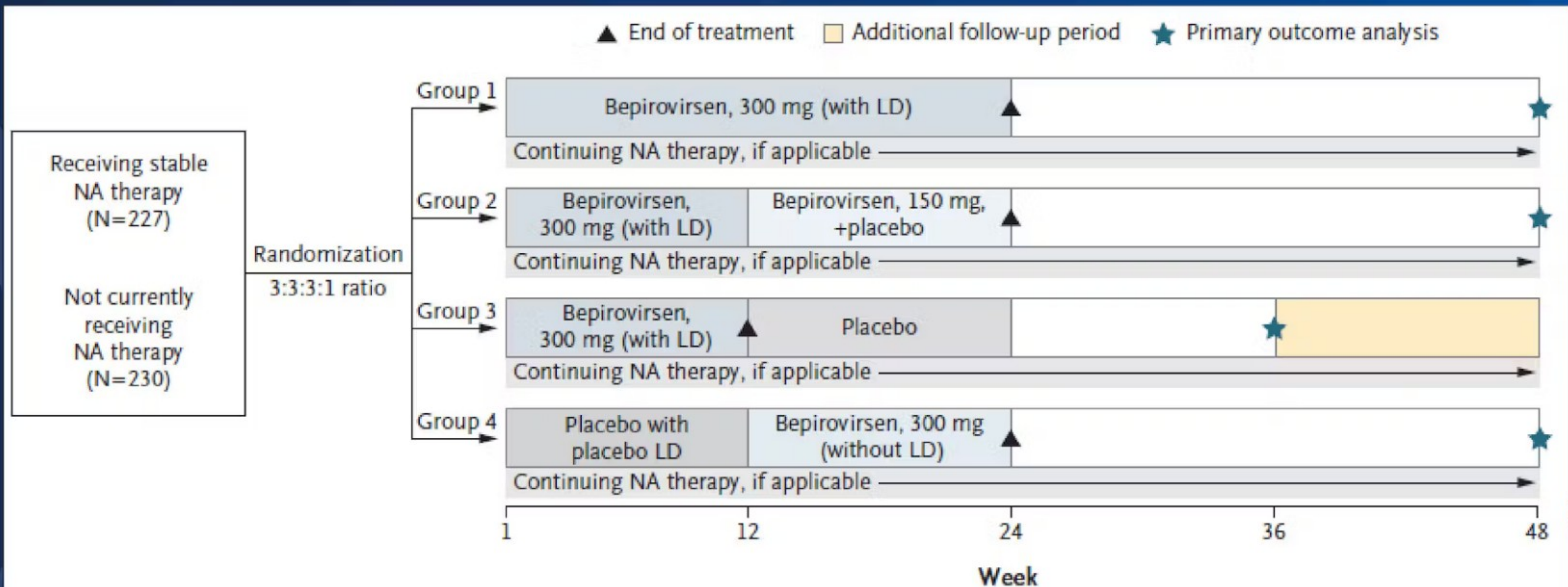


Figure 1. Trial Design.

Take Home Points

1. HBV has a huge health impact on global and domestic populations, who are often at-risk and underserved.
2. Universal HBV screening is now recommended, along with more inclusive HBV vaccination guidelines.
3. **Evolving HBV treatment algorithms and new antiviral therapies are transforming clinical care and the opportunities for clinical, research, and scholarly activity.**





Thank You!

Questions?

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What questions or comments to you have?

Very good presentation! Would love to see HBV testing encouraged more.

What do you think about routine antibody testing after vaccine series ?

Great Presentation, thank you for such a wide scope of information. I feel has become a tool, that I can use when encountering newly diagnosed or co-infected HBV& HIV persons.

Great Presentation!!

none very good presentation

Great presentation!