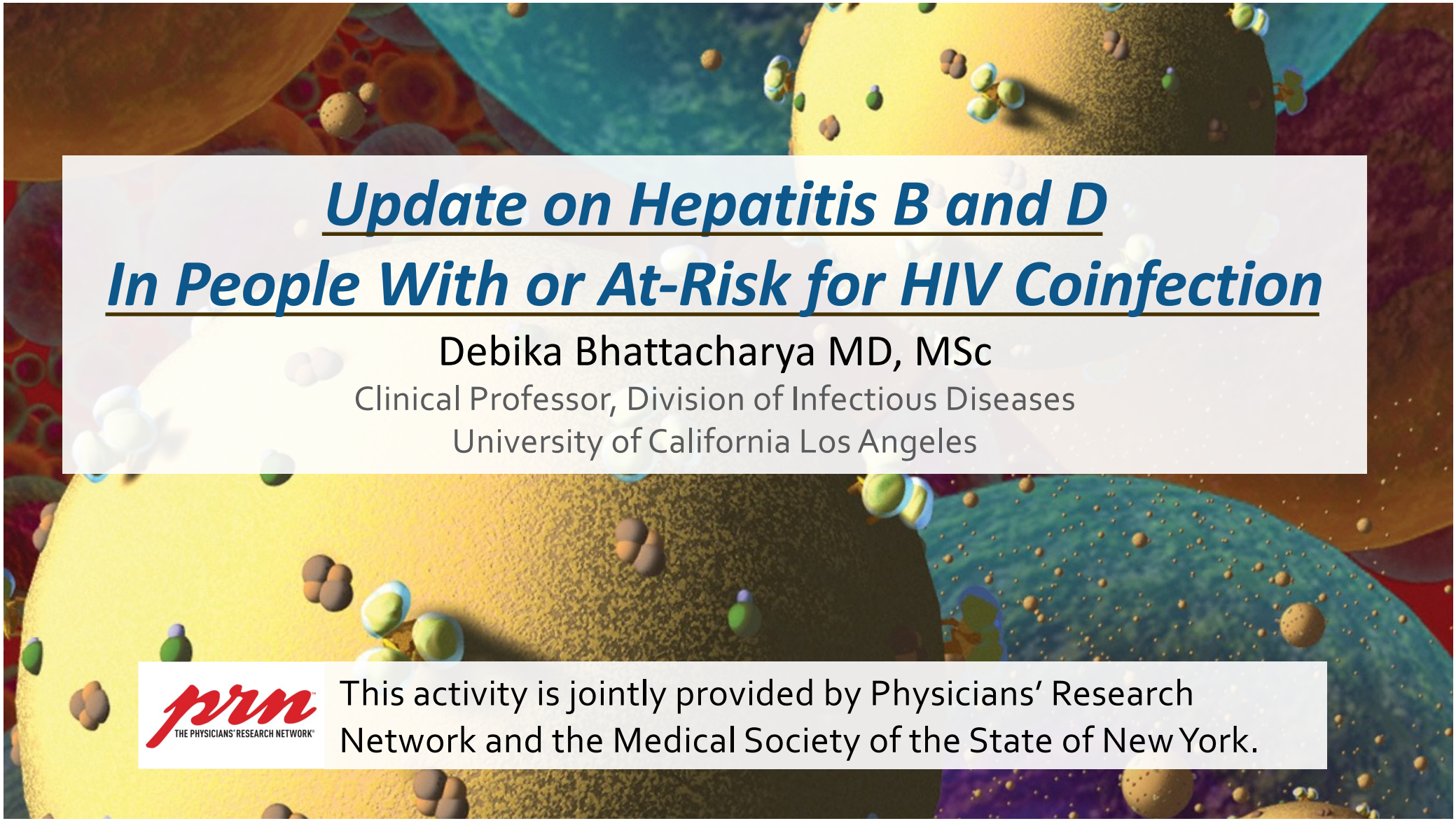

Update on Hepatitis B and D In People With or At-Risk for HIV Coinfection

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University of California Los Angeles

This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

Disclosures

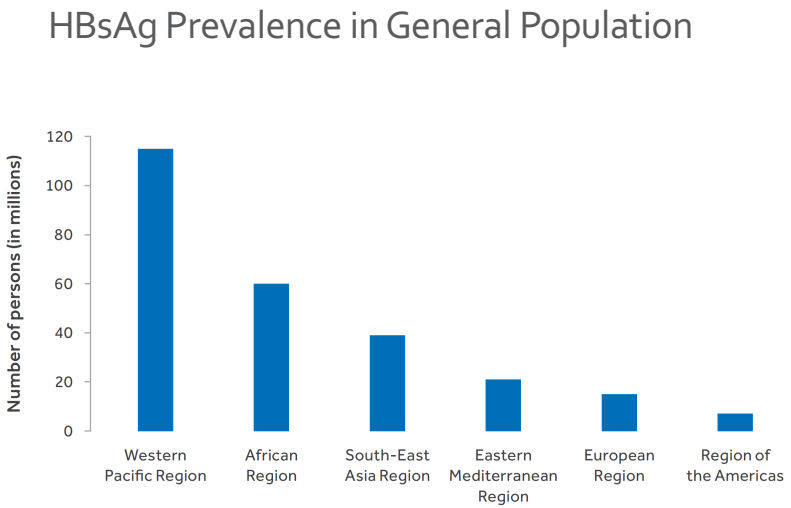
- Gilead Sciences research grant support to institution

Objectives

- Risk Factors for HBV and HDV Infection
- HBV Prevention Strategies in PLWH
  - Newer Vaccines
  - Management of Isolated Anti-HBc
  - Considerations in PrEP
- Management of HBV Coinfection and PLWH
  - TAF vs TDF
  - Incomplete Suppression
  - Unintended Consequences of Treatment Cessation
- Novel Therapies for HBV and HDV

Global Status of HBV Infection

- 2015--257 million people living with chronic HBV infection;
  - 68% in African and Western Pacific regions
- **7.4% of persons with HIV also have HBV coinfection (2.7 million persons)**
- Hepatocellular cancer (HCC) is 3rd most common cause cancer mortality globally
  - HBV → 40% of liver cancers



WHO Global Hepatitis Report. 2017, GBD Report 2016.

HBV Infection Globally and in the US

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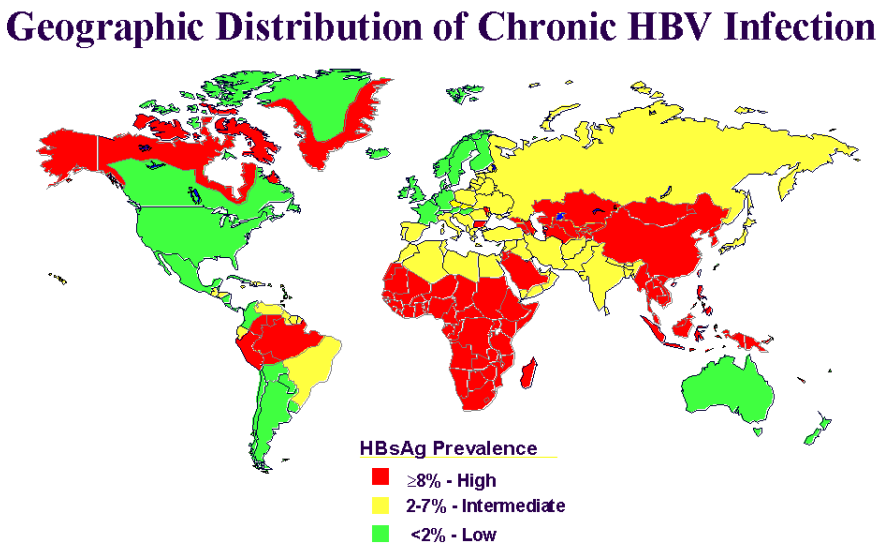

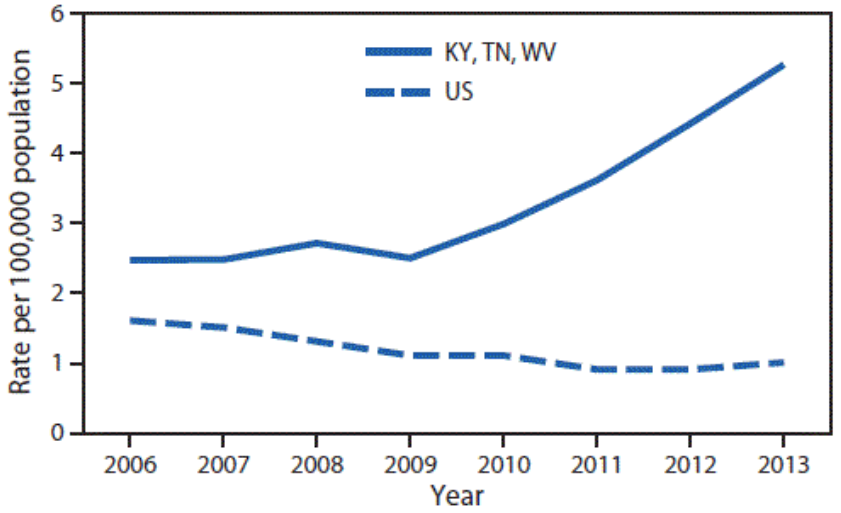

Abbreviations: KY = Kentucky; TN = Tennessee; US = United States; WV = West Virginia;.

FIGURE 1. Incidence of acute hepatitis B virus infection, by year—United States and Kentucky, Tennessee, and West Virginia, 2006–2013

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Global Prevalence and Impact of HDV Infection

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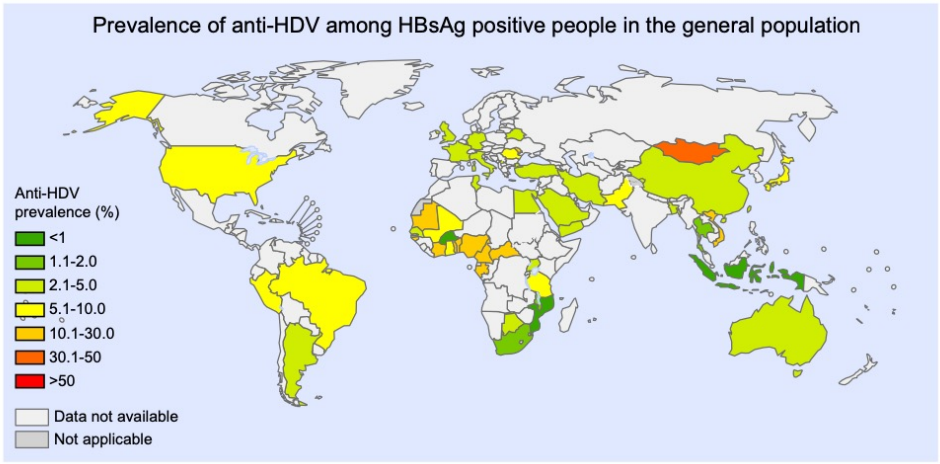

- HDV prevalence: 4.5% (95% CI 3.6–5.7)
- HDV prevalence higher PWID, HCV, HIV
- HDV causes
  - 18% of cirrhosis
  - 20% of HCC

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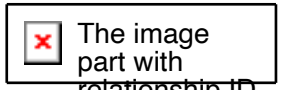
Stockdale J Hepatology 2020

Transmission Risk Factors for HBV and HDV



- HBV
  - Perinatal Transmission
  - Sexual Transmission
  - Injection Drug Use
  - Sharing contaminated items with blood- toothbrushes, razors, glucose monitor
- HDV
  - Perinatal Transmission (rare)
  - Sexual Transmission
  - Injection Drug Use
  - Sharing contaminated items

Natural History of HBV

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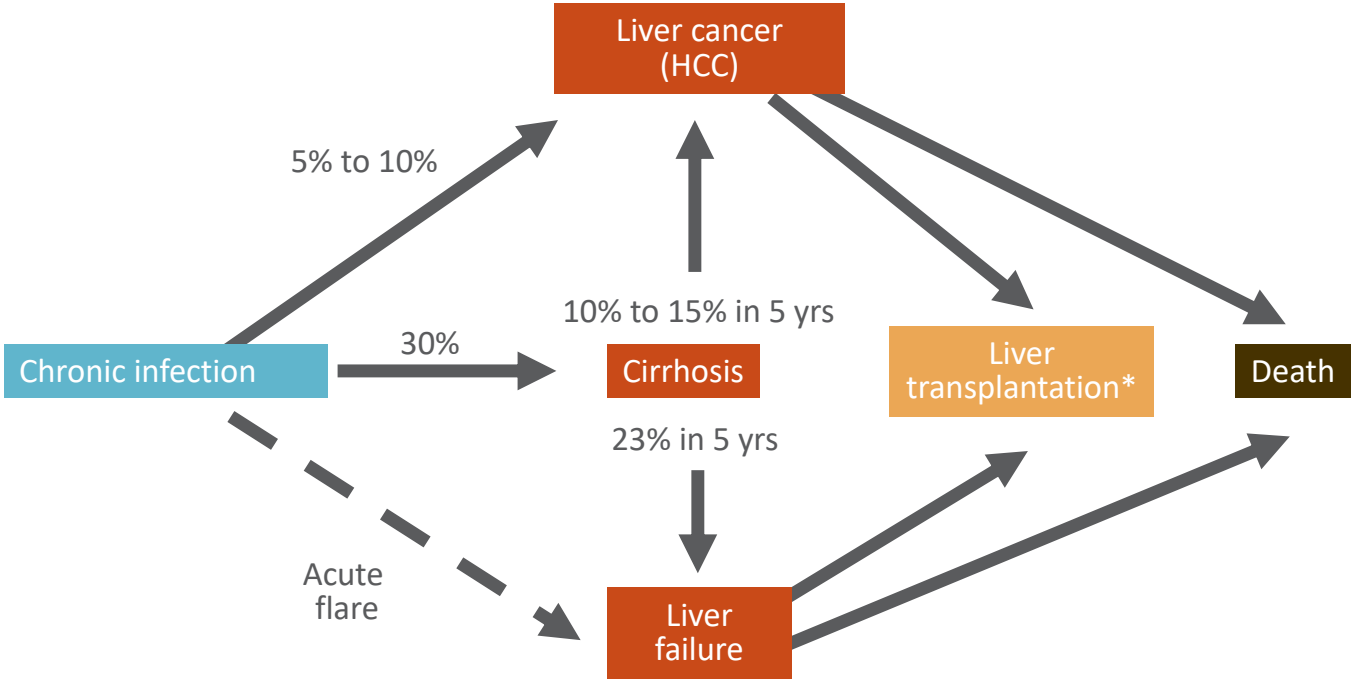

*HBV is the 6th leading cause of liver transplantation in the United States.

Fattovich G, et al. Gastroenterology. 2004;127:S35-S50. Seeff LB, et al. Hepatology. 2001;33:455-463. Torresi J, et al. Gastroenterology. 2000;118:S83-S103. Fattovich G, et al. Hepatology. 1995;21:77-82.

HBV Life Cycle

Virologic:
Establishment of latent reservoir (cccDNA and integrated HBV DNA)

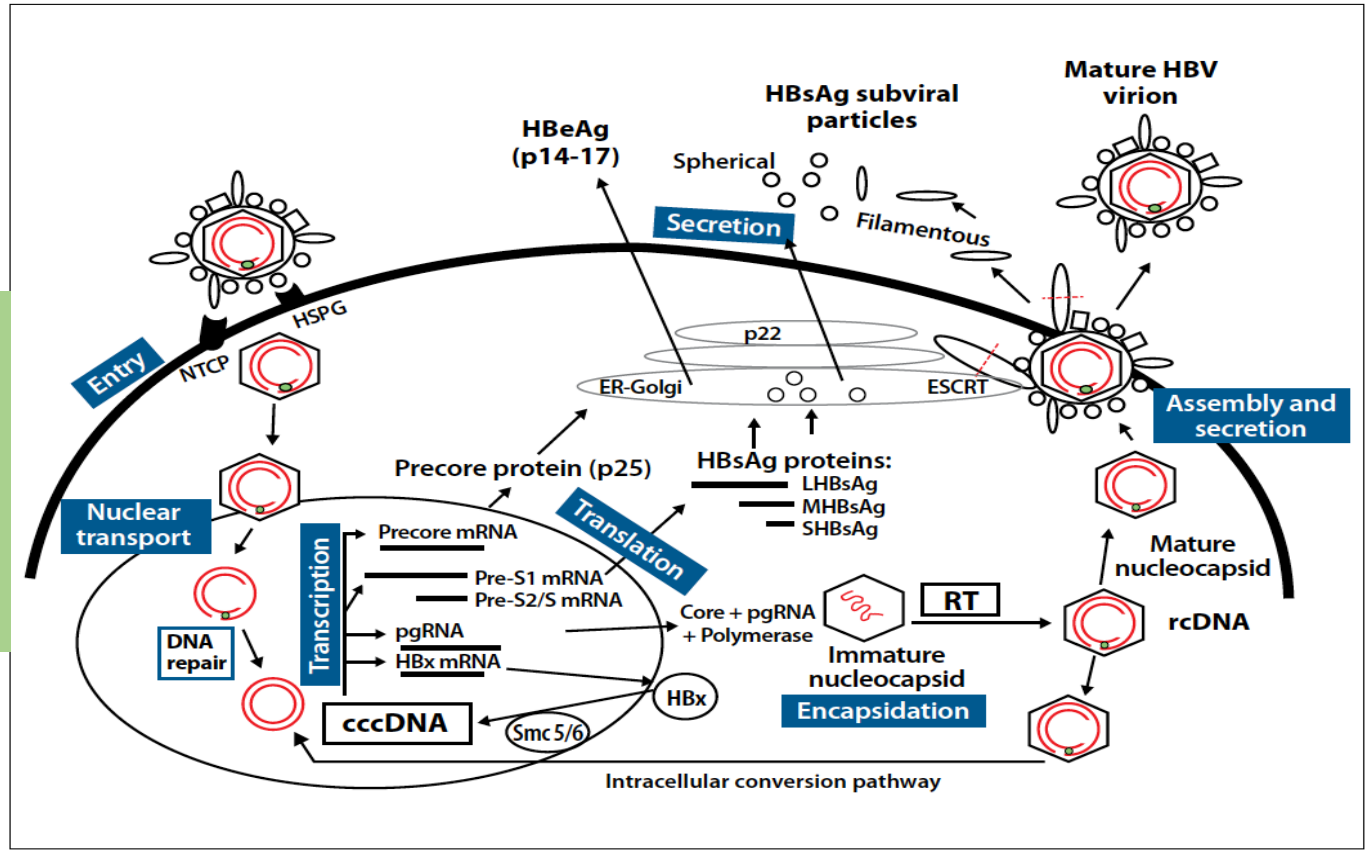

Figure. Life cycle of hepatitis B virus.

Immune:
Defective Immune Response

- HBV specific CD8 responses
- HBV specific B cell responses
- Innate Immunity

Peters Gastro Hep 2017

Impact of HIV on HBV Disease Progression

- Higher levels of HBV replication (HBV DNA & HBeAg+)[1]
- Higher mortality when compared to HIV or HBV monoinfection[2]
- Higher rate of chronicity[2,3]
  - 20 to 80% as compared to 3-5% in HIV -
  - risk increases with lower CD_4 at time of HBV acquisition
- Lower ALT levels[4]
- Faster progression to cirrhosis
- Higher incidence of lamivudine resistance

1. Bodsworth NJ et al. J Infect Dis 1989 2. Thio et al Lancet 2002 2. Bodsworth NJ, et al. J Infect Dis 1991. 3. Hadler SC et al. J Infect Dis 1991. 4. Gilson RJ et al. AIDS 1997.

Hepatitis B Serology

- HBsAg
  - Protein on surface of HBV detected during acute or chronic HBV infection
  - Presence indicates an individual is INFECTED
- Anti-HBs
  - Presence indicates recovery and IMMUNITY from HBV infection
  - Also develops following vaccination against hepatitis B

- Total anti-HBc (antibody to HBV core antigen)
  - Appears at the onset of symptoms in acute hepatitis and persists for life
  - Presence indicates EXPOSURE (previous or ongoing infection with HBV)

Lok AS, et al. Hepatology. 2009;50:661-662.

Hepatitis B Serology: HBeAg Status in CHB Patients

- HBeAg
  - Secreted coproduct of nucleocapsid gene of HBV found in serum during acute and chronic HBV with wild-type infection
  - Presence indicates replicating natural variant virus and often associated with high HBV DNA levels

- Anti-HBe
  - Produced by immune system temporarily during acute HBV infection or consistently during or after a burst in viral replication in setting of wild-type infection clearance
  - Conversion from HBeAg positive to anti-HBe positive a predictor of
    - Long-term clearance of HBV in patients undergoing antiviral therapy and indicates lower levels of HBV

Other Markers in HBV Management and Cure

- ALT
  - Marker of liver inflammation
  - "New" normal or "healthy" ALT: < 30 U/L for men and < 19 U/L for women[1]
  - Presence of 1 normal value does not exclude significant disease or subsequent complications
- HBV DNA
  - Marker of HBV viral replication
  - Predicts development of cirrhosis and HCC[2,3]
  - Interpret in conjunction with ALT and/or histology
- cccDNA
  - covalently closed circular DNA, reservoir of HBV infection in hepatocyte

1. Lok AS et al. Hepatology. 2009;50:661-662. 2. Iloeje UH et al. Gastroenterology. 2006;130:678-686.
3. Chen CJ et al. JAMA. 2006;295:65-73.

Interpretation of HBV Serologic Results

HBsAg	Total Anti-HBc	Anti-HBs	Interpretation
Negative	Negative	Negative	Susceptible; offer vaccination
Negative	Positive	Positive	Immune due to natural infection
Negative	Negative	Positive	Immune due to hepatitis B vaccination
Positive	Positive	Negative	Chronic HBV infection
Negative	Positive	Negative	Unclear; could be any one of the following: 1. Resolved infection (most common) 2. False-positive anti-HBc; susceptible 3. “Low-level” chronic infection 4. Resolving acute infection

CDC. Hepatitis B FAQs for health professionals. Available at: http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm.

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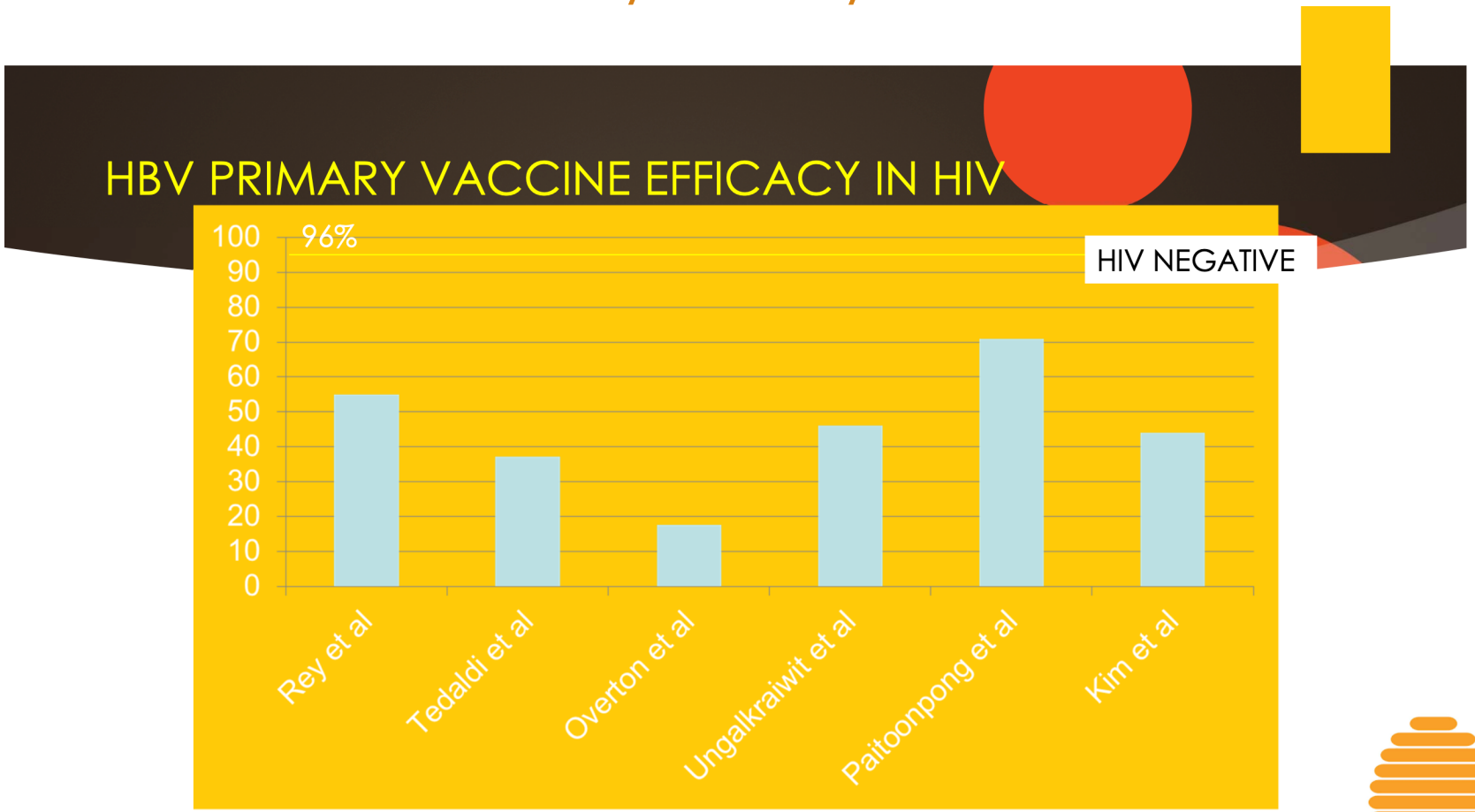
CDC. Hepatitis B FAQs for health professionals. Available at: http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm.

HBV Primary Efficacy in HIV



Slide courtesy K Sherman

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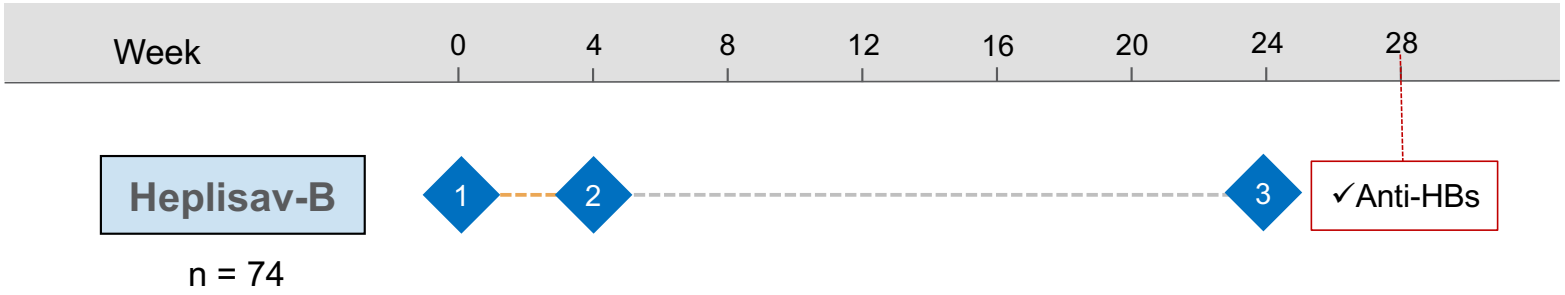
Heplisav-B: Vaccine-Naïve Adults with HIV (Group B) Bee-HIVe Trial (ACTG 5379): Study Design



n = 74

Inclusion Criteria
On ART >56 days prior to entry
CD4 >100 cells/mm^3
HIV RNA <1000 copies/ml

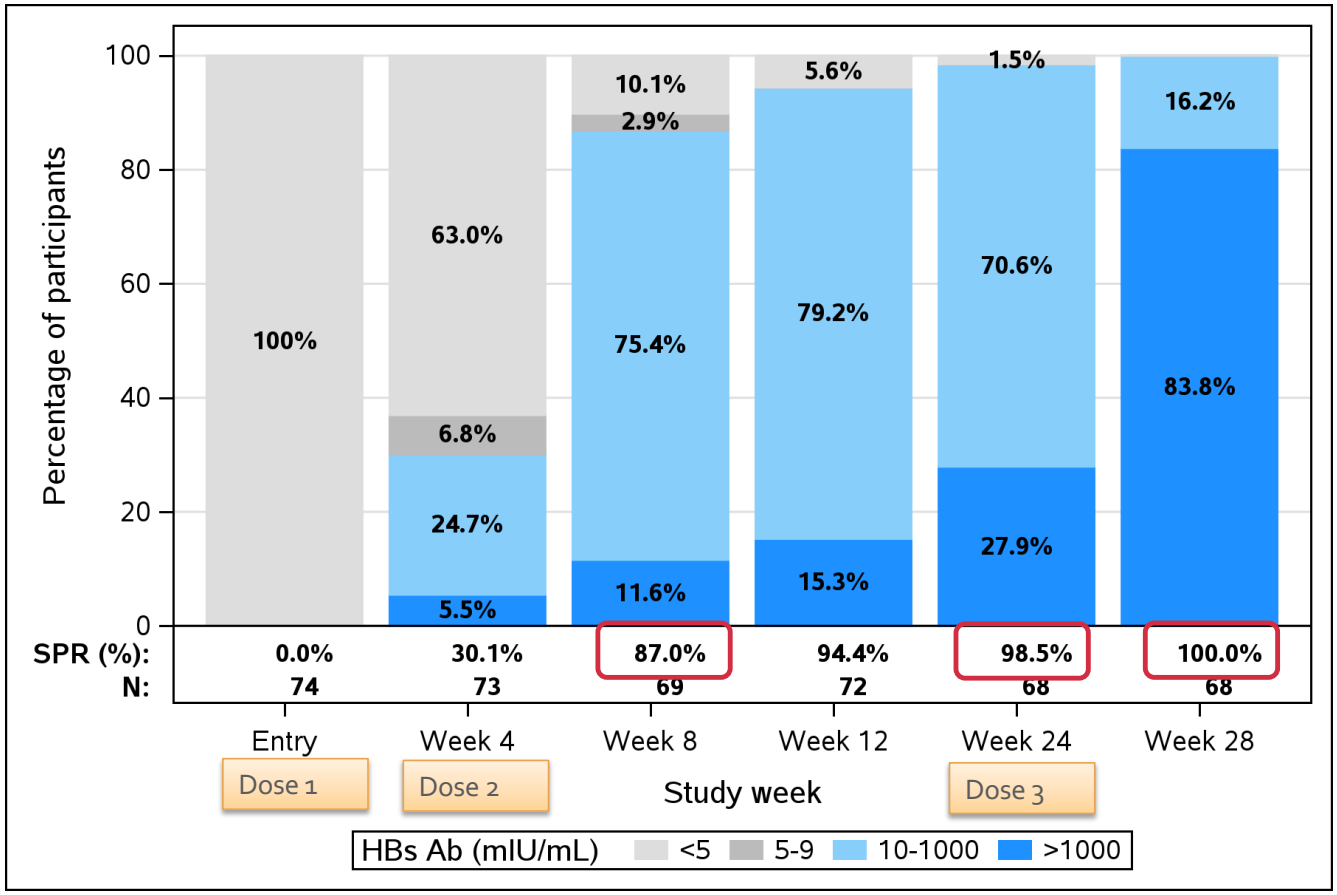
Exclusion Criteria
Prior HBV immunization
HBsAg or anti-HB core (+)
Immunocompromising condition

Vaccine Dosing
Heplisav-B: 0.5 mL dose of 3 mg CpG adjuvant with 20 mcg recombinant HBsAg

Marks et al, IDWeek 2022, Washington DC. Abstract LB749.

Heplisav-B: Vaccine-Naïve Adults with HIV (Group B)
Bee-HIVe Trial (ACTG 5379): Seroprotective Response by Study Week

The image part with relationship ID rId7 was not found in the file.

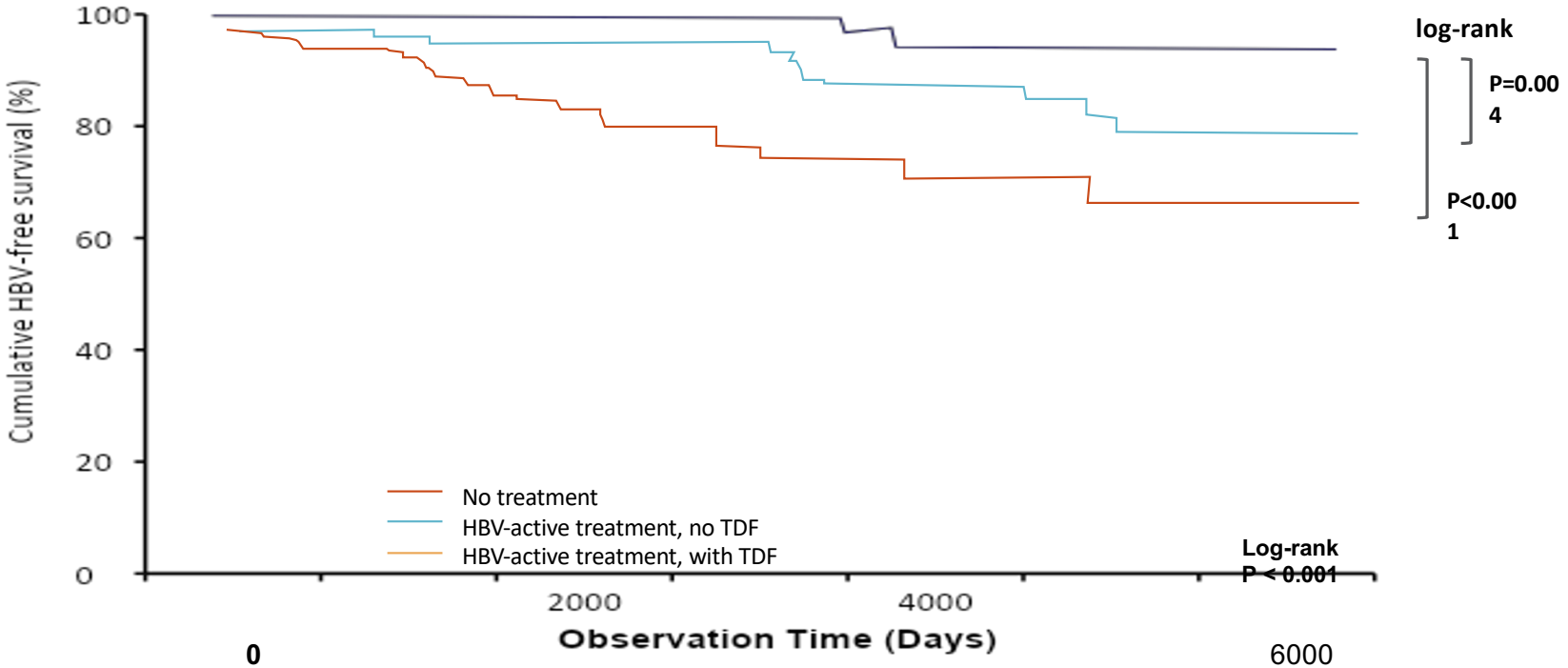


Marks et al, IDWeek 2022, Washington DC. Abstract LB749.

DHHS Guidelines on HBV Vaccination in PLWH

Status	Vaccines
Primary Vaccination	1. 40 mcg (Engerix, double dose at 0,1, 6 months) 2. Heplisav-B at 0,1 months
Non-Responders	1. 40 mcg (Engerix, double dose at 0,1, 6 months) 2. Heplisav-B at 0,1 months 3. Some may wait for $CD4 \geq 200$
Timing for Booster	1. Anti-HBs <10mIU/ml

Protective Effect of HBV-active ART Against Incident HBV Infection



Numbers in observation	0			6000
No treatment	107	50	19	8
Treatment, no TDF	86	67	36	16
Treatment, with TDF	189	49	38	12

Brinkman K et al. CROI 2013; O#33;
Heuft MM et al., AIDS 2014;28:999–1005

Interpretation of HBV Serologic Results

HBsAg	Total Anti-HBc	Anti-HBs	Interpretation
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CDC. Hepatitis B FAQs for health professionals. Available at: http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm.

Lack of anamnestic response with isolated anti-HBc

	Anti-HBs titer, IU/L			
Baseline status (no. of subjects)	**1-9**	**10-99**	**100-999**	**≥1000**
Anti-HBc negative (40)	0 (0)[a]	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.

[a] $P = .004$

Gandhi JID 2005

HBV Vaccination Recommendations: Isolated Anti-HBc

DHHS Recommendations

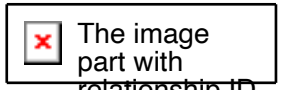
- -One standard dose of HBV Vaccine
- -Anti-HBs at 1-2 months post dose
- If titer is >100 mIU/ml, no further vaccination necessary
- If titer is < 100 mIU/ml, complete series should be completed followed by anti-HBs testing
- Rationale: 100% of patients with isolated anti-HBc who achieved a titer of 100 mIU/mL after a booster dose maintained an anti-HBs response for >18 months as compared to only 23% of those who achieved a titer of 10 to 100 mIU/mL

Alternative Approach:

- Initiate full series

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection
Piroth JID 2016

Considerations During PrEP- HBV Infection



- Does patient need treatment of HBV (outside of PrEP) ?
- Does patient have cirrhosis?

Guidelines: When to Start HBV Therapy

Guidelines	HBeAg Positive			HBeAg Negative		
	HBV DNA, IU/mL	ALT	Liver Disease	HBV DNA, IU/mL	ALT	Liver Disease
AASLD[1]	> 20,000	≥ 2 x ULN	N/A	≥ 2000	≥ 2 x ULN	N/A
	N/A	N/A	Cirrhosis	N/A	N/A	Cirrhosis

For those who need HBV therapy: HBV therapy should continue past PrEP discontinuation

1. Terrault NA, et al. Hepatology. 2016;63:261-283.

Guidelines: When to Start HBV Therapy

Guidelines	HBeAg Positive			HBeAg Negative		
	HBV DNA, IU/mL	ALT	Liver Disease	HBV DNA, IU/mL	ALT	Liver Disease
AASLD[1]	> 20,000	≥ 2 x ULN	N/A	≥ 2000	≥ 2 x ULN	N/A
	N/A	N/A	Cirrhosis	N/A		

Refer to ID/GI experienced in HBV Management

For those who need HBV therapy: HBV therapy should continue past PrEP discontinuation

1. Terrault NA, et al. Hepatology. 2016;63:261-283.

OPEN

The Safety of Tenofovir–Emtricitabine for HIV Pre-Exposure Prophylaxis (PrEP) in Individuals With Active Hepatitis B

Marc M. Solomon, MD, MPH,† Mauro Schechter, MD, PhD,‡ Albert Y. Liu, MD, MPH,†§ Vanessa M. McManhan, MS,* Juan V. Guanira, MD, MPH,‖ Robert J. Hance, AA,* Suwat Chariyalertsak, MD, DrPH,¶ Kenneth H. Mayer, MD,# and Robert M. Grant, MD, MPH,*† for the iPrEx Study Team*

(*J Acquir Immune Defic Syndr* 2016;71:281–286)

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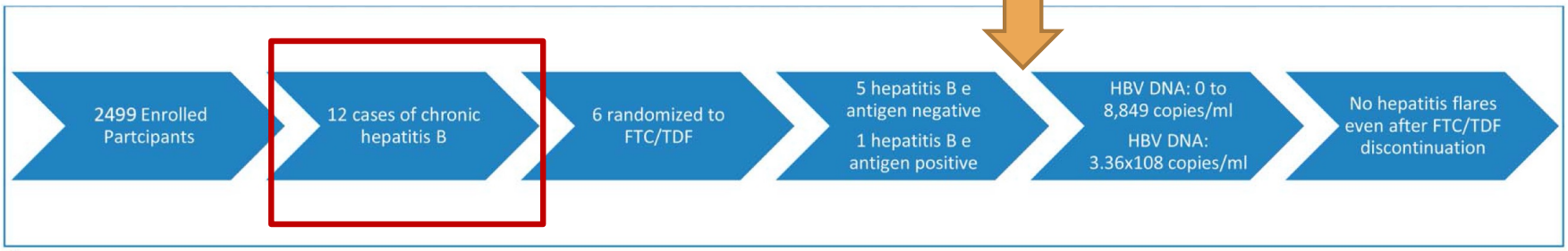
Followed 4,8,12 weeks after stopping TDF/FTC

Excluded if met local care thresholds, cirrhosis, ALT/AST/tbili>2 ULN



- 1/5 patients had ALT elevation (grade 1) at week 12
- No evidence of TDF or FTC resistance
- HBV Antiviral Therapy Discontinuation Well Tolerated

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PrEP with TDF/FTC Protects Against Incident HBV in MSM

Figure 1. Flow chart of MSM with and without PrEP

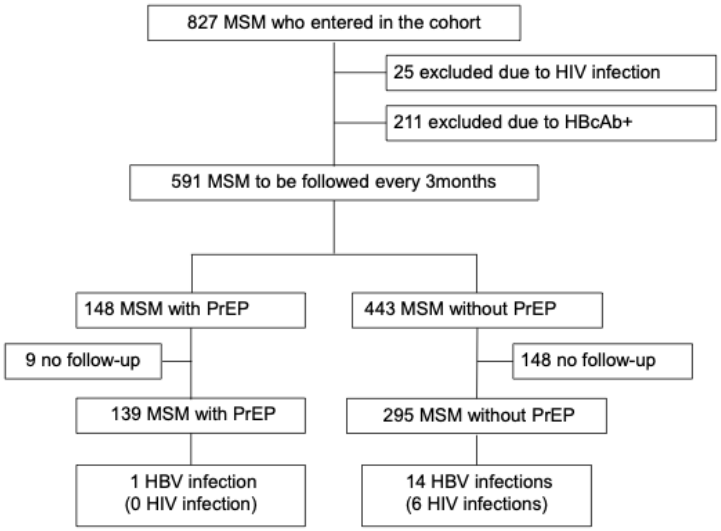
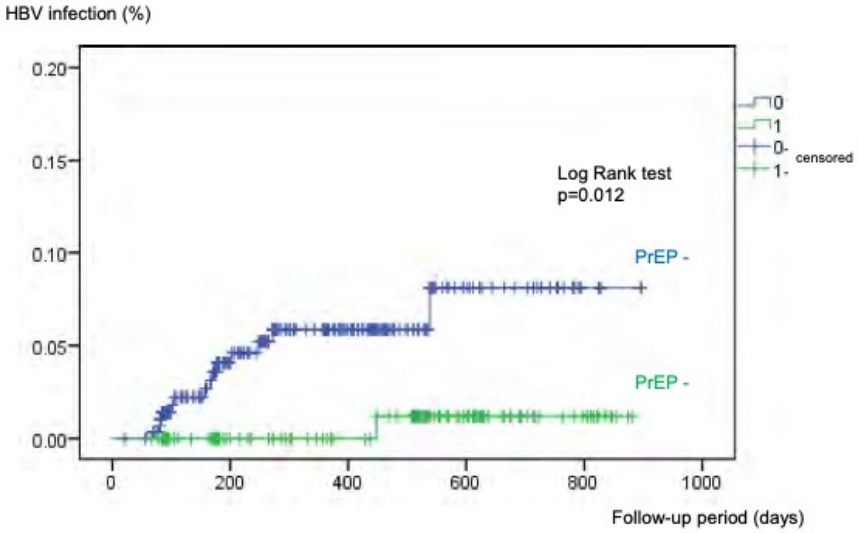


Figure 2. Preventive effect of PrEP against HBV infection by Kaplan-Meier



HR 0.12 between PREP and no PREP
88% reduction in likelihood of acquiring HBV

3 HBV infections acquired in those with anti-HBs>10

Mizushima D CROI 2020.

Interpretation of HBV Serologic Results

HBsAg	Total Anti-HBc	Anti-HBs	Interpretation
Negative	Negative	Negative	Susceptible; offer vaccination
Negative	Positive	Positive	Immune due to natural infection
Negative	Negative	Positive	Immune due to hepatitis B vaccination
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CDC. Hepatitis B FAQs for health professionals. Available at: http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm.

Diagnosis and Approach to Management in HBV Coinfection

H&P	Routine Lab Tests	Serology/Virology	Imaging/Staging Studies
Age, duration of disease, Sx/signs of cirrhosis	CBC incl plt	HBsAg, anti-HBc, anti-HBs	Abdominal ultrasound
ETOH, smoking, other SUD	AST/ALT/tbili/alk phos/albumin/INR	HBeAg/anti-HBe	Transient elastography or serum fibrosis panel (APRI, FIB-4, Fibrotest)
Renal/bone comorbidities	Chem 7 (incl Cr)	HBV DNA	Liver biopsy in select cases
Family history of HCC	Tests to r/o other causes of chronic liver disease	HAV, HCV	
Vaccination Status	AFP, GGT, CD4, HIV-1 VL	HDV, HBV genotype?	

Current HBV Treatment Recommendations

The image part with relationship ID rId7 was not found in the file.

Recommendations for Treating Hepatitis B Virus Infection

Indication for Therapy

- For all people with HIV/HBV coinfection, including pregnant people, regardless of CD4 count and HBV DNA level **(AIII),** therapy should be selected that includes drugs active against both HIV and HBV infections **(AIII).**

Preferred Therapy (CrCl ≥60 mL/min)

- The ART regimen must include two drugs active against HBV, preferably with (TDF 300 mg plus [FTC 200 mg or 3TC 300 mg]) or (TAF [10 or 25 mg][a] plus FTC 200 mg) PO once daily **(AII).**

Preferred Therapy (CrCl 30–59 mL/min)

- The ART regimen must include two drugs active against HBV, preferably with TAF (10 or 25 mg)[a] plus FTC 200 mg PO once daily **(AII).**

Preferred Therapy (CrCl <30 mL/min, Not Receiving HD)

- Renally dosed entecavir (in place of TDF or TAF), *or*
- ART with renally dose-adjusted TDF and FTC **(BIII)** when recovery of renal function is unlikely (see Table 6 for dosing recommendation for TDF and FTC or 3TC for people with renal impairment). Guidance for TAF use in people with CrCl <30 is not yet established.

Preferred Therapy (Receiving HD)

- (TDF or TAF) plus (FTC or 3TC) can be used. Refer to Table 6 for dosing recommendation.

Duration of Therapy

- People on treatment for HBV and HIV should receive therapy indefinitely **(BIII)**.

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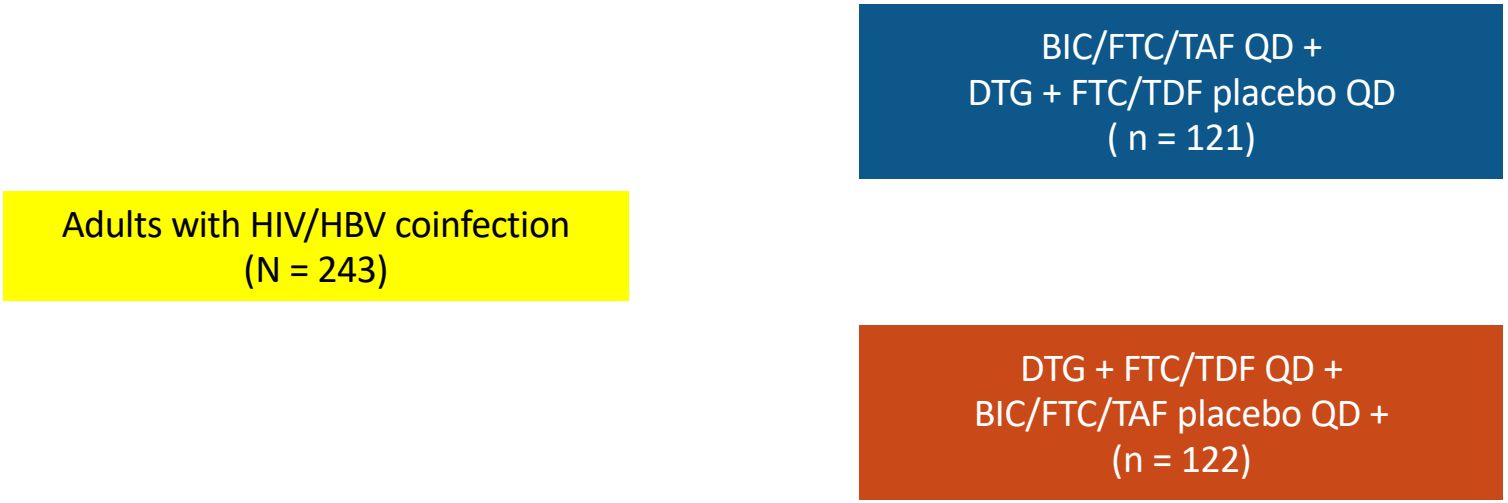
ALLIANCE Study

- Randomized, placebo-controlled phase III study



Participants from 11 countries in Asia, Europe, North, and Latin America
Approximately 30% HIV-1 RNA >100,000 c/mL and approximately 40% had a CD4+ cell count <200 cells/mm^3 at baseline.
Median HBV DNA was 8.1 log10 IU/mL, and 78% were HBeAg positive

TAF Superior to TDF for HBV Parameters?

Result	BIC/FTC/TAF (n = 119)	DTG + FTC/TDF (n = 122)
HBV, n (%)		
▪ HBV DNA <29 IU/mL†	75 (63.0)	53 (43.4)
▪ HBV DNA ≥29 IU/mL	43 (36.1)	66 (54.1)
▪ No virologic data	1 (0.8)	3 (2.5)
HBsAg		
▪ Loss	15/119 (12.6)	7/121 (5.8)
▪ Seroconversion	10/119 (8.4)	4/121 (3.3)
HBeAg		
▪ Loss	23/90 (25.6)	14/97 (14.4)
▪ Seroconversion	21/90 (23.3)	11/97 (11.3)
ALT normalization	44 (73.3)	26 (55.3)

High Rates of HBV Functional Cure HIV/HBV

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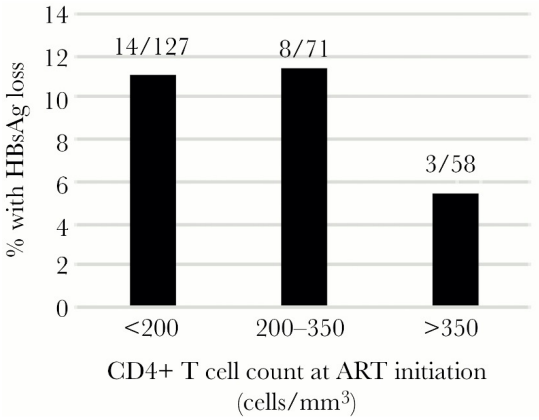
- 10% HBsAg loss after 2 years of TDF in Zambian Cohort
- ~10% HBsAg loss over 9 years in US Cohort
- 18% HBsAg loss after median follow-up 11 years in German cohort
  - median time to HBsAg loss was ~3.5 years
- All cohorts: HBsAg loss associated with low CD4 count
- Ethnicity may also be important
- Immune reconstitution in setting of low CD4 counts may be responsible for "immune boost"

Low CD4 count at Initiation Associated with HBsAg Loss



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Chihota JID 2020, Jain MK CROI 2019, Boesecke CROI 2019

Evaluation and Monitoring for HIV/HBV Coinfection

- HBV DNA at baseline and q 3-6 mos after initiating therapy
- HBeAg/anti-HBe q6 mos/qyr (DB)
- HBsAg/anti-HBs q yr (DB)
- Electrolytes and Cre at baseline and q3-6 mos
- Urinalysis q 6 mos
- HAV vaccination
- HCV Evaluation

DHHS OI Guidelines

Incomplete HBV Suppression Common in PLWH

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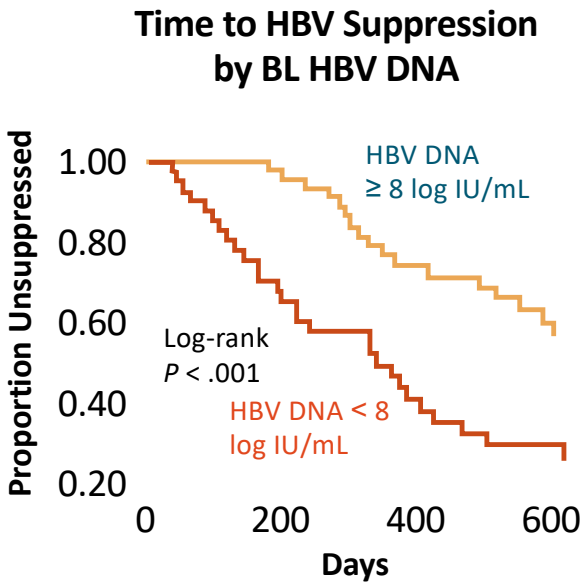
- Retrospective cohort study in US of 133 patients with HIV/HBV coinfection and HBV viremia
- Tenofovir-based ART initiated; HBV DNA measured at 1 yr
- 54% (95% CI: 46% to 63%) had incomplete HBV DNA suppression at 1 yr
  - Incomplete suppression associated with BL HBV DNA level > 8 IU/mL (adjusted OR: 3.21; 95% CI: 1.39-7.43)



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Hafkin. J Viral Hepatitis. 2014;21:288.

HBV Virologic Failure Associated with Increased Risk of HCC; even with ND HIV!

TABLE 4. Risk of HCC Associated With Time-Updated HBV DNA Level and Time-Updated Detectable HIV and HBV Status Among Persons Coinfected With HIV/HBV Who Had Quantitative or Qualitative HBV DNA Assessed in the NA-ACCORD (1995-2016) (n = 5,316; 87 Incident HCC Events Identified)

Characteristic	No. Exposed*	No. Events	Person-Time	Incidence Rate (95% CI), Events/1,000 Person-Years	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)
Time-updated HBV DNA						
Undetectable	3,656	44	22,692	1.9 (1.4-2.6)	Reference	Reference
Detectable	3,364	43	12,850	3.3 (2.4-4.5)	1.87 (1.22-2.85)	2.22 (1.42-3.47)
Time-updated detectable HIV and HBV status‡						
Undetectable HIV and HBV	3,494	42	19,164	2.2 (1.6-3.0)	Reference	Reference
Detectable HIV, undetectable HBV	1,881	2	3,529	0.6 (0.07-2.0)	0.29 (0.07-1.21)	0.27 (0.06-1.14)
Undetectable HIV, detectable HBV	2,835	27	8,510	3.2 (2.1-4.6)	1.55 (0.95-2.52)	1.77 (1.07-2.92)
Detectable HIV and HBV	2,480	16	4,340	3.7 (2.1-60)	1.93 (1.07-3.49)	2.21 (1.17-4.18)

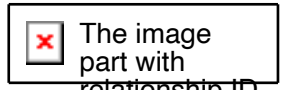
Kim Hepatology 2020

HCC Surveillance in PLH and HBV

- Cirrhosis
- Asian males older than age 40
- Asian females older than age 50
- Family history of HCC
- Males older than age 20 who are from sub-Saharan Africa.
- Some experts screen patients with HIV/HBV coinfection over **40 years of age**.

Marrero Hepatology 2018. DHHS OI Guidelines

Considerations In ART Regimens Without HBV Activity



- Importance of HBsAg Screening at Baseline and Prior to Switch
- 3TC alone is not sufficient for HBV therapy

Considerations In ART Regimens Without HBV Activity

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- Importance of HBsAg Screening at Baseline and Prior to Switch

BRIEF REPORT: CLINICAL SCIENCE

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]

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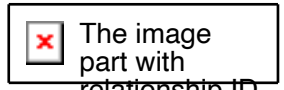
HBV Treatment Cessation Trials- HBeAg Negative

Name	Number of Participants	Duration of f/u	HBsAg Loss	Rebound HBV Viremia	Hepatitis Flares or Adverse Events
Finite Study	42	144 weeks	Higher in cessation		Adverse Events: Tx Cessation 19% vs 0 in Continuation
STOP Study (Toronto)	67	72 weeks	Similar: 2% vs 5%	98% in cessation vs 5% in tx continuation	Hepatitis Flare: 53% tx cessation vs 5% in continuation
STOP-NUC	158	96 weeks	10% in tx cessation		14% had to re-initiate rx
RETRACT-B observational	1552	4 yrs		83%	61% with ALT flares, Hepatic Decompensation 1%

Considerations In ART Regimens Without HBV Activity



- Importance of HBsAg Screening at Baseline and Prior to Switch
- 3TC alone is not sufficient for HBV therapy

Incidence of Lamivudine Resistance in Persons with HBV Infection

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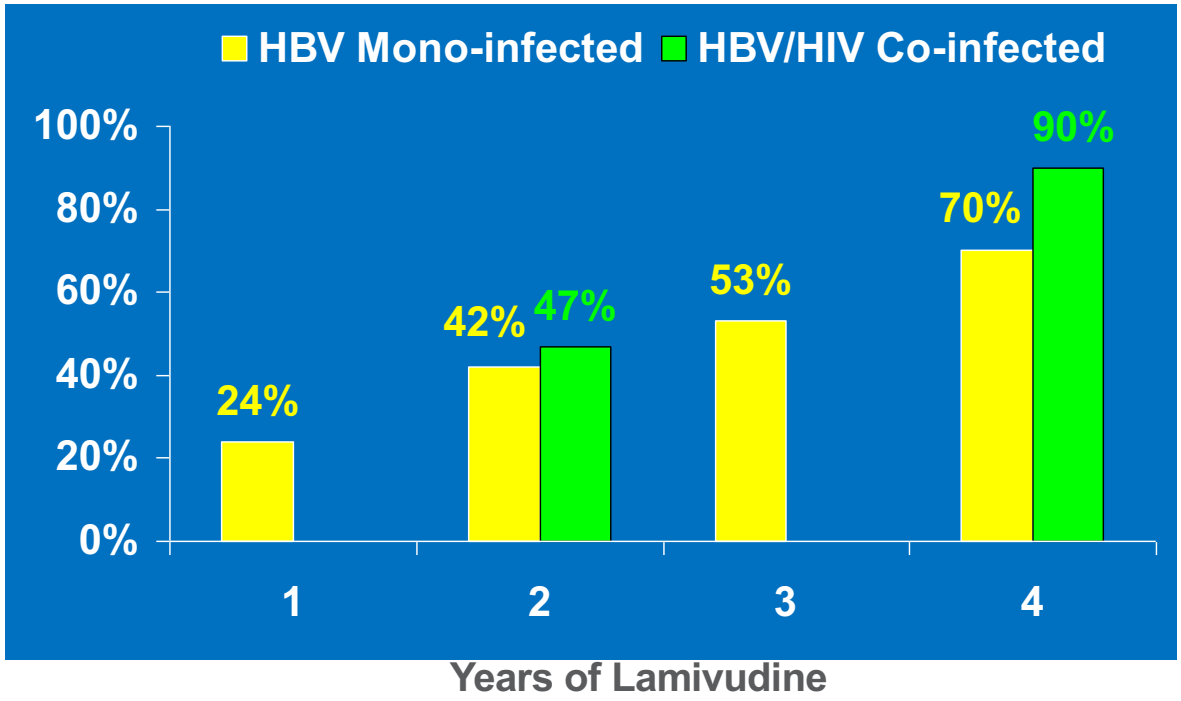

Lai C et al. Clin Inf Dis 2003;36:687
Chang T et al. Antiviral therapy 2000;5:44A.

Leung NWYet al. J Hepatology 1999;30:59 A
Benhamou Y et al. Hepatology 1999; 30:1302-6.

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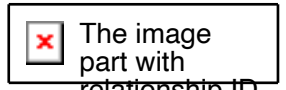
Considerations In ART Regimens Without HBV Activity

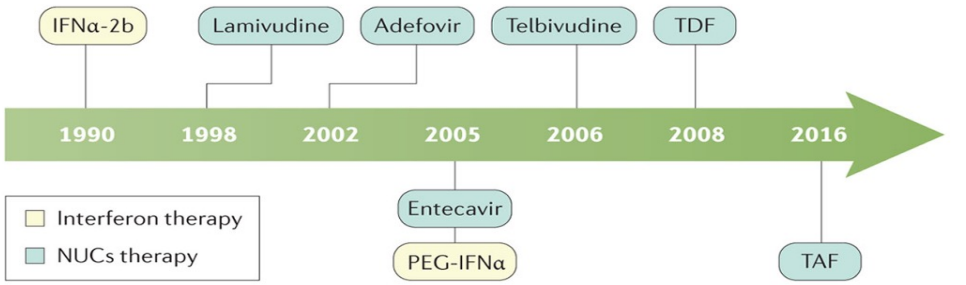


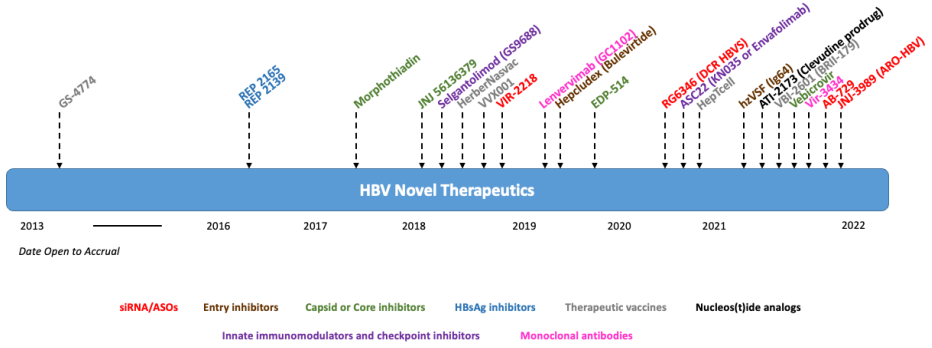
- Data-free Zone: Isolated anti-HBc in PLH
- My practice: HBV Vaccination, monitoring closely with switch

Novel HBV Therapeutics

1990 - 2016

2016 - now





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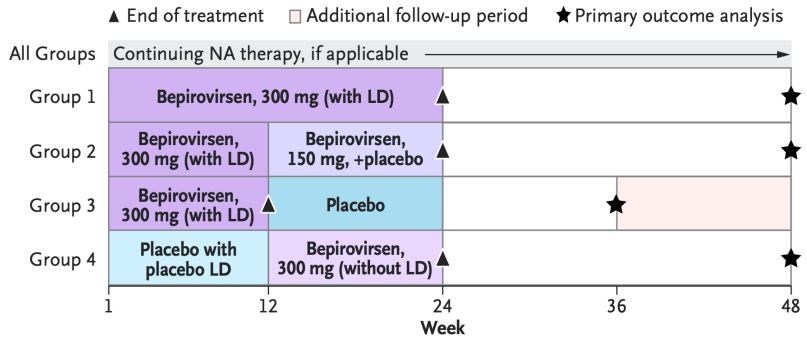
Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection

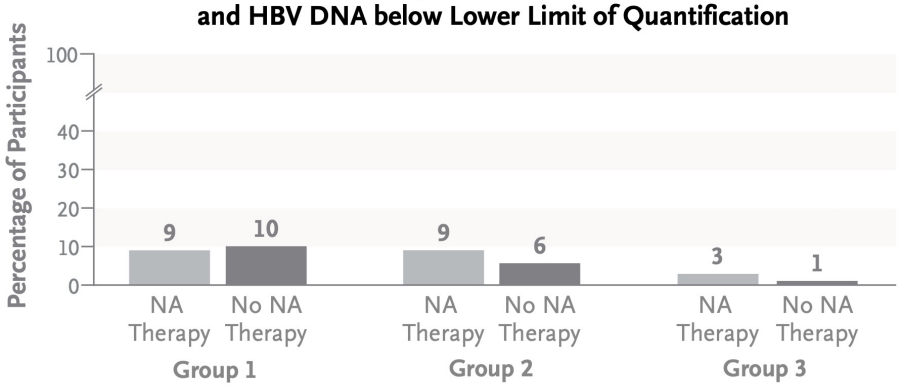
Yuen M-F et al. DOI: 10.1056/NEJMoa2210027

Trial Design



Loading dose (LD) of bepirovirsen (300 mg, in groups 1, 2, and 3) or placebo (in group 4) on days 4 and 11.

Patients with HBsAg below Lower Limit of Detection and HBV DNA below Lower Limit of Quantification



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Novel Therapeutics for HDV

	Lonafarnib	Bulevirtide
Mechanism	Prenylation ihnhibitor	Entry inhibitors
Duration (weeks)	48	48
Adverse Events	GI: nausea, diarrhea	Bile acid increases: 20-fold
Tx Discontinuation Due to AEs	20%	very few
Undetectable HDV RNA	10% (20%)	15%
>2 Log HDV RNA	15 % (30%)	60-70 %
ALT normalization	25% (35%)	50%
HBsAg loss	few	0%

Jachs et al APT 2022, Loglio et al J Hepatol 2022, Herta et al Pathogens 2022, Wedemeyer et al MYR301 ILC 2022, Dietz-Fricke et al JHEPR in press 2023, Fontaine et al ILC 2022, Degasperi et al ILC 2022, Bazinet et al Lancet 2017 , Etzion et al HDIN 2023, Degasperi et al HDIN 2023

Summary

- Adjuvanted hepatitis B vaccine (Heplisav) shows promise in PLWH
- TAF vs TDF in HIV/HBV: Higher rates of HBsAg loss and HBeAg loss but too soon to tell whether this is superior
- Incomplete HBV DNA Suppression Common in HIV/HBV
  - Residual HBV Viremia Confers HCC Risk
- HBV-Active ART Cessation is Not Recommended in HIV/HBV
- Novel Therapeutics For HBV Are on the Horizon!


Thank You for Your Attendance!
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