Hepatitis B Prevention: New vaccines and the boundaries of HBV protection

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Disclosures

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Disclaimer

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Objectives

- Describe the newer options for hepatitis B immunization and their seroprotective efficacy in key subpopulations including people with HIV.
- Summarize our current understanding of the role of antiviral therapy in HBV prevention.

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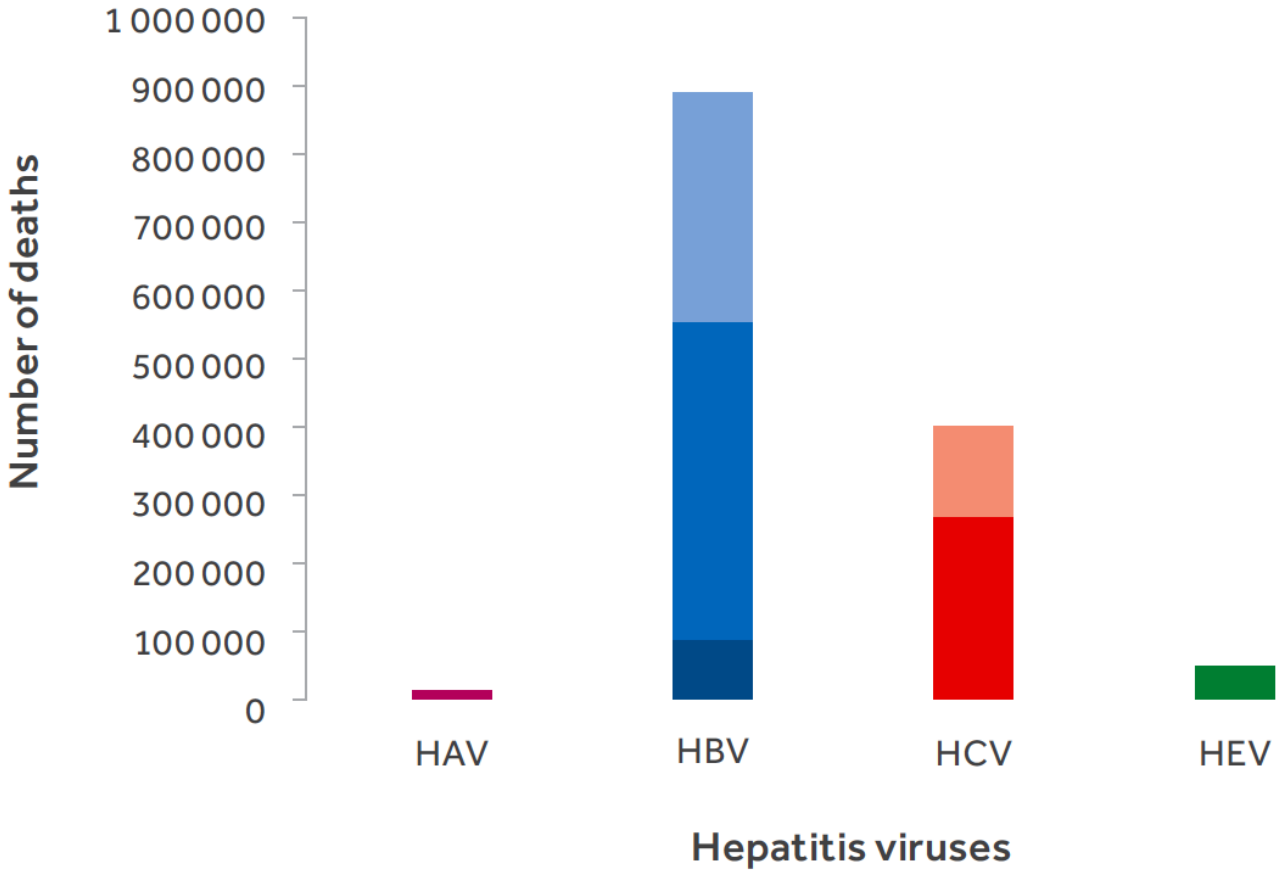
Hepatitis B remains a major public health issue

- Leading cause of liver-related deaths worldwide
- Of 296 million w/ chronic HBV infection, only ~10% aware of diagnosis
- People with HIV at greater risk of HBV infection, chronic HBV & complications
- Rates of HBV vaccine uptake have been suboptimal



WHO Global Hepatitis Report, 2017

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Case 1: To Vaccinate or Not?

25-year-old man with HIV infection, CD4 count of 190 cells/mm^3 and virally suppressed in tenofovir DF-emtricitabine and dolutegravir is here for routine care. Has had multiple male partners in the past 2 months and would like STI screening. On review of labs, you note that his anti-HBc, anti-HBs and hepatitis B surface Ag are all negative.

What would you do next?

A. Wait for CD4 >200 cells/mm^3 before starting HBV immunization series.

B. Immunize with double-dose recombinant hepatitis B vaccine (*Engerix*).

C. Don't bother to immunize for HBV since he's currently on tenofovir.

D. Immunize with CpG-adjuvanted HBV vaccine (*Heplisav-B*).

E. Immunize with 3-antigen HBV vaccine (*PreHevbrio*).

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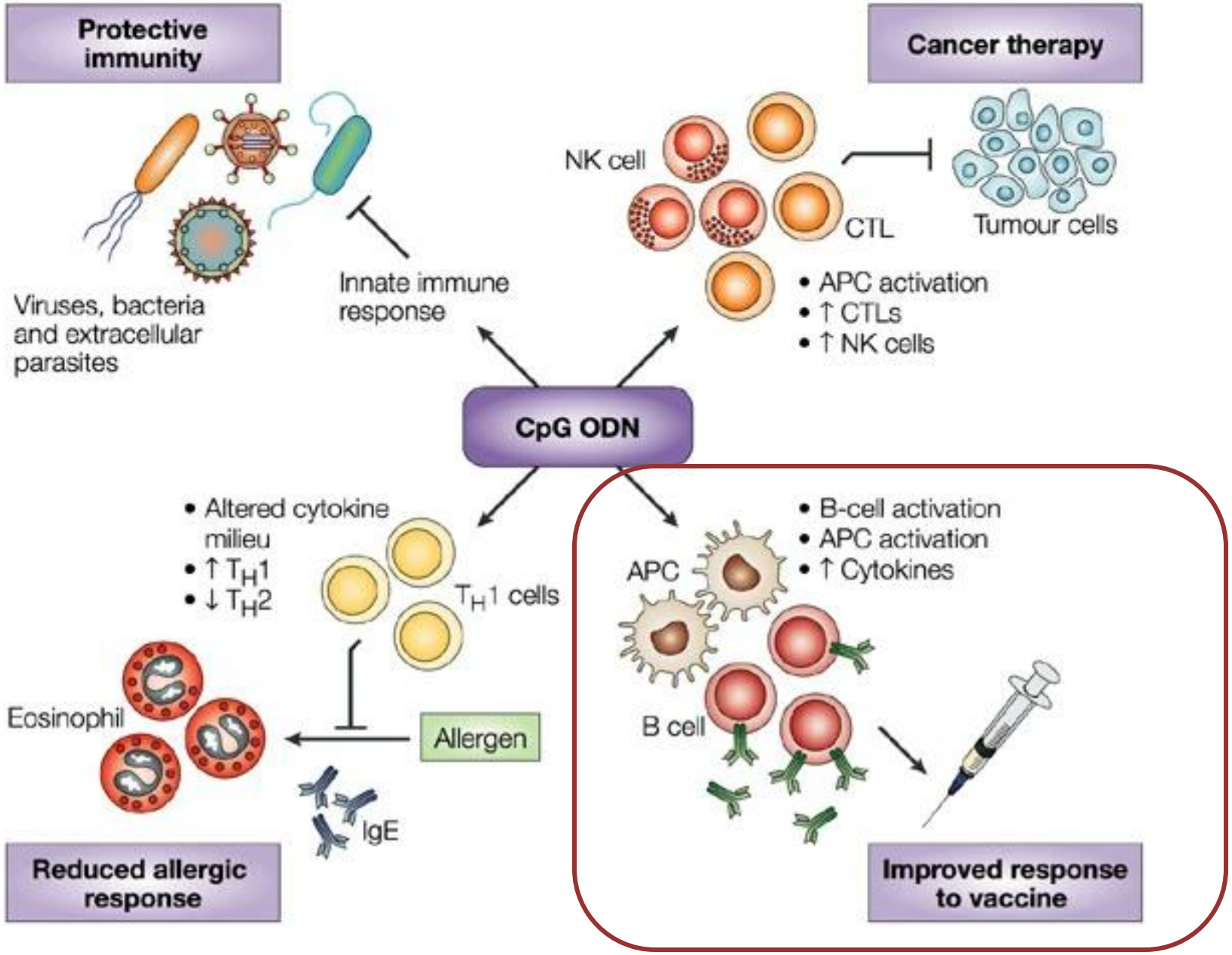
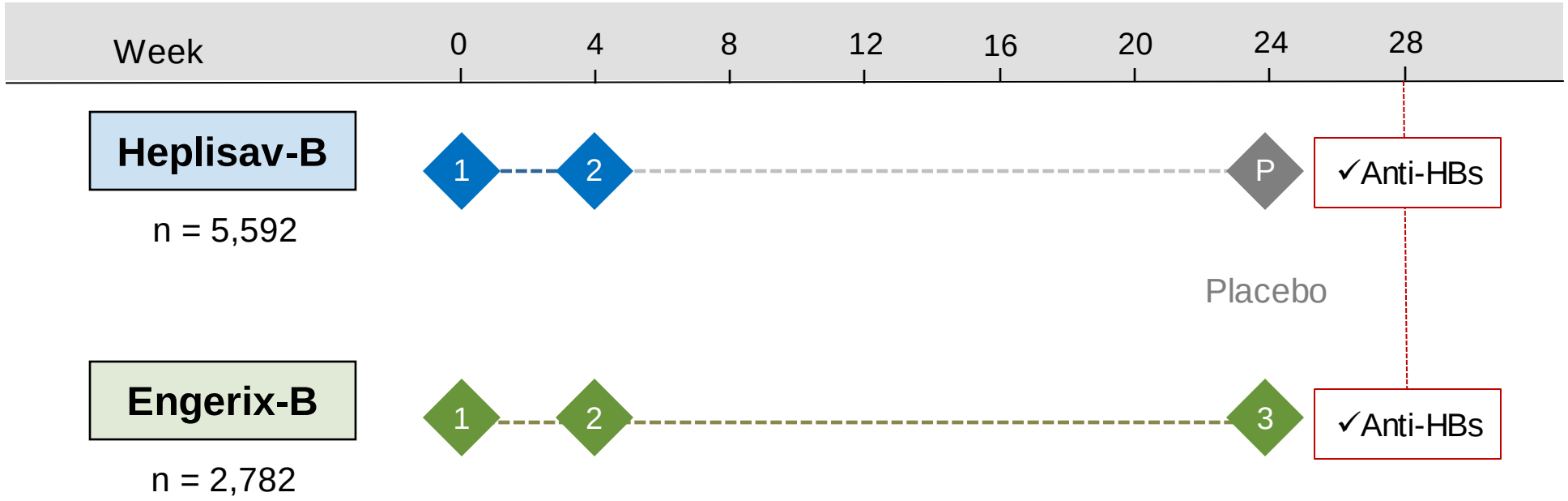
CpG-adjuvanted HBV vaccine (*Heplisav-B*)



Klinman, D. Immunotherapeutic uses of CpG oligodeoxynucleotides. *Nat Rev Immunol* 4, 249–259 (2004).

Heplisav-B vs. Engerix-B in Adults 18-70 Years of Age HBV-23 Trial: Study Design



Participants

HBV naïve adults ≥18

Exclusions: HBV, HIV, pregnancy or lactation, chronic steroid use, autoimmune condition

Vaccine Dosing

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

Engerix-B: 1 mL dose of 20 mcg recombinant HBsAg with **aluminum adjuvant**

Source: Jackson S, et al. Vaccine. 2018:36:668-74.

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Heplisav-B vs. Engerix-B in Adults 18-70 Years of Age Baseline Characteristics

Baseline Characteristic	Heplisav-B (n = 5,592)	Engerix-B (n = 2,782)
Age, mean (SD), years	50.4 (11.7)	50.4 (11.7)
Male, no. (%)	2845 (51)	1391 (50)
Race, no. (%)		
White	3972 (71)	2007 (72)
Black	1462 (26)	697 (25)
Asian	57 (1)	38 (1.4)
American Indian/Alaskan Native	60 (1)	24 (1)
Other	41 (1)	16 (0.6)
Body mass index (BMI), mean (SD), kg/m^2	31 (7.5)	31 (7.6)
BMI ≧30 kg/m^2, n (%)	2728 (49)	1286 (46)
Smoker, n (%)	1844 (33)	909 (33)
Diabetes type 2, n (%)	763 (13.6)	381 (13.7)

Source: Jackson S, et al. Vaccine. 2018:36:668-74.

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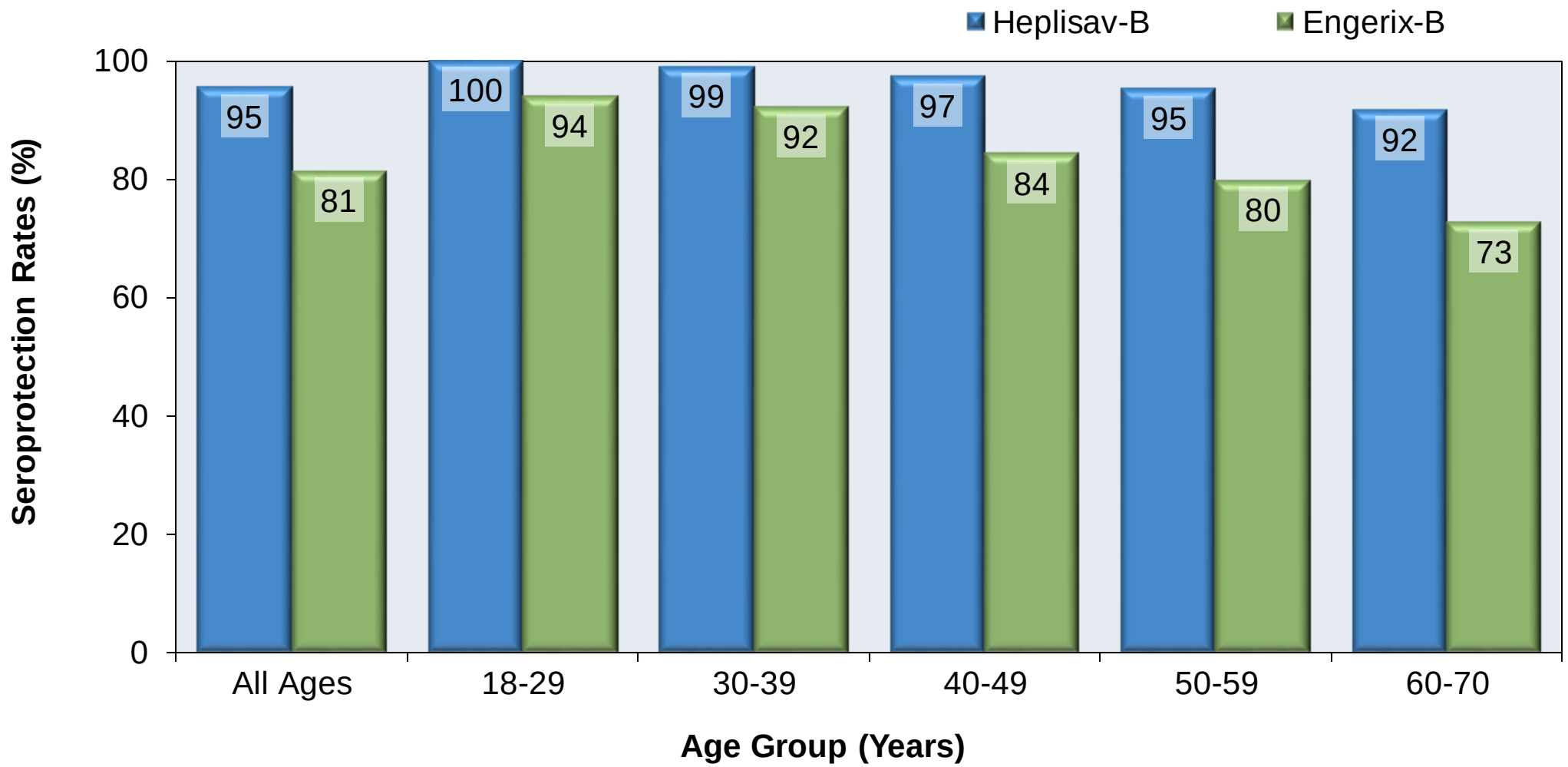
Heplisav-B vs. Engerix-B in Adults 18-70 Years of Age Seroprotection Rates, by Age Group



Source: Jackson S, et al. Vaccine. 2018:36:668-74.

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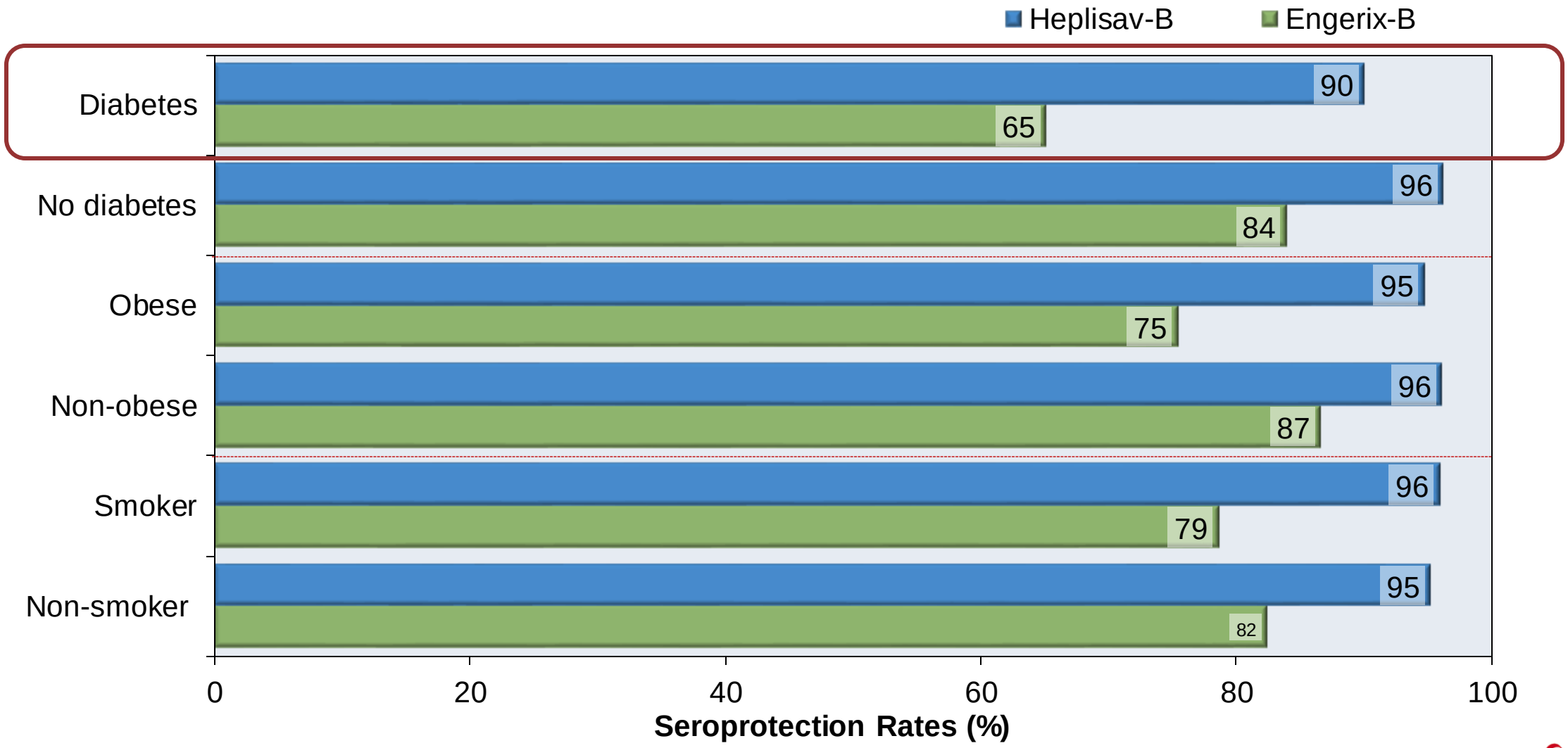
Heplisav-B vs. Engerix-B in Adults 18-70 Years of Age Seroprotection Rates, by Comorbidities



Source: Jackson S, et al. Vaccine. 2018:36:668-74.

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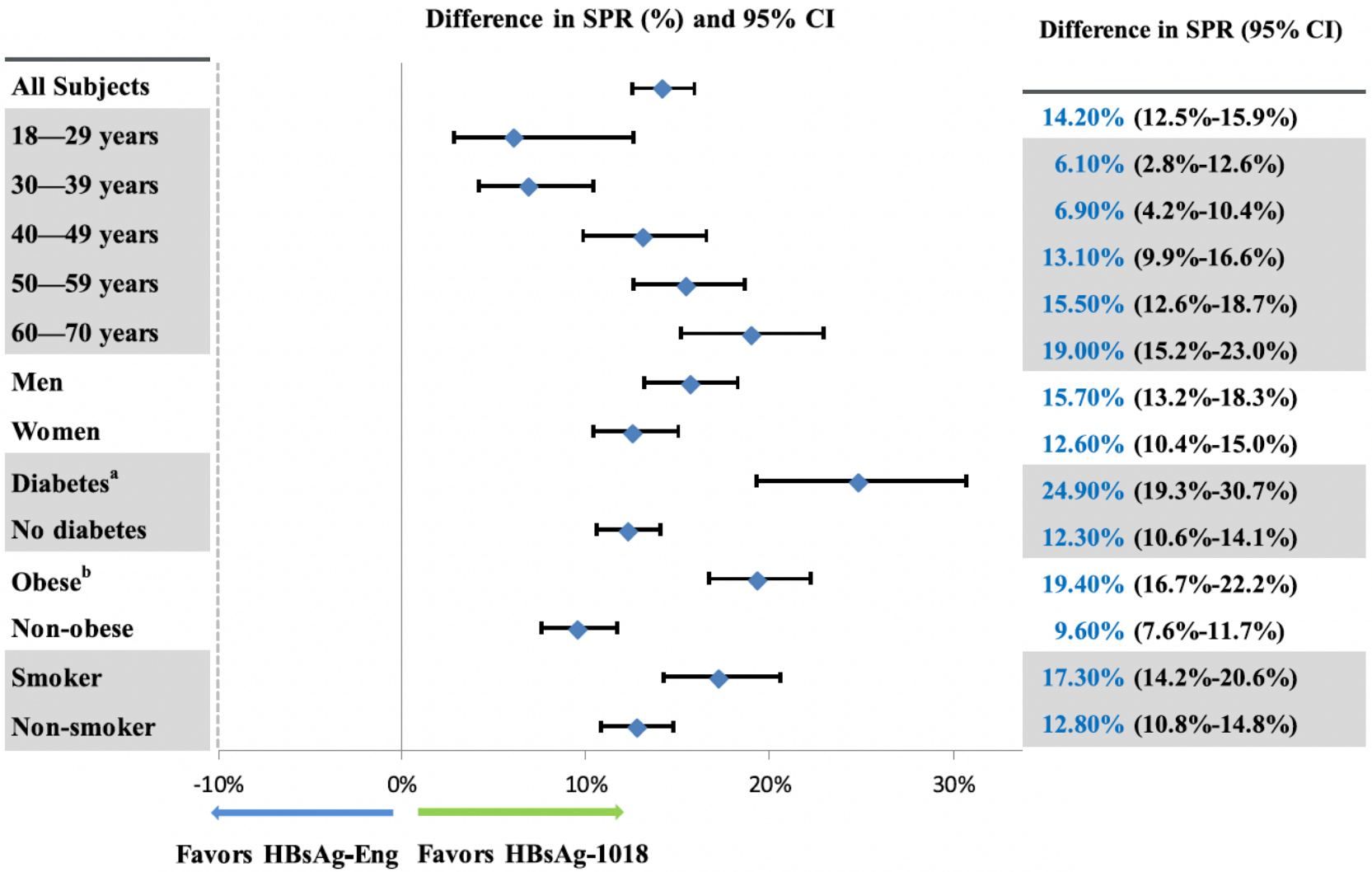
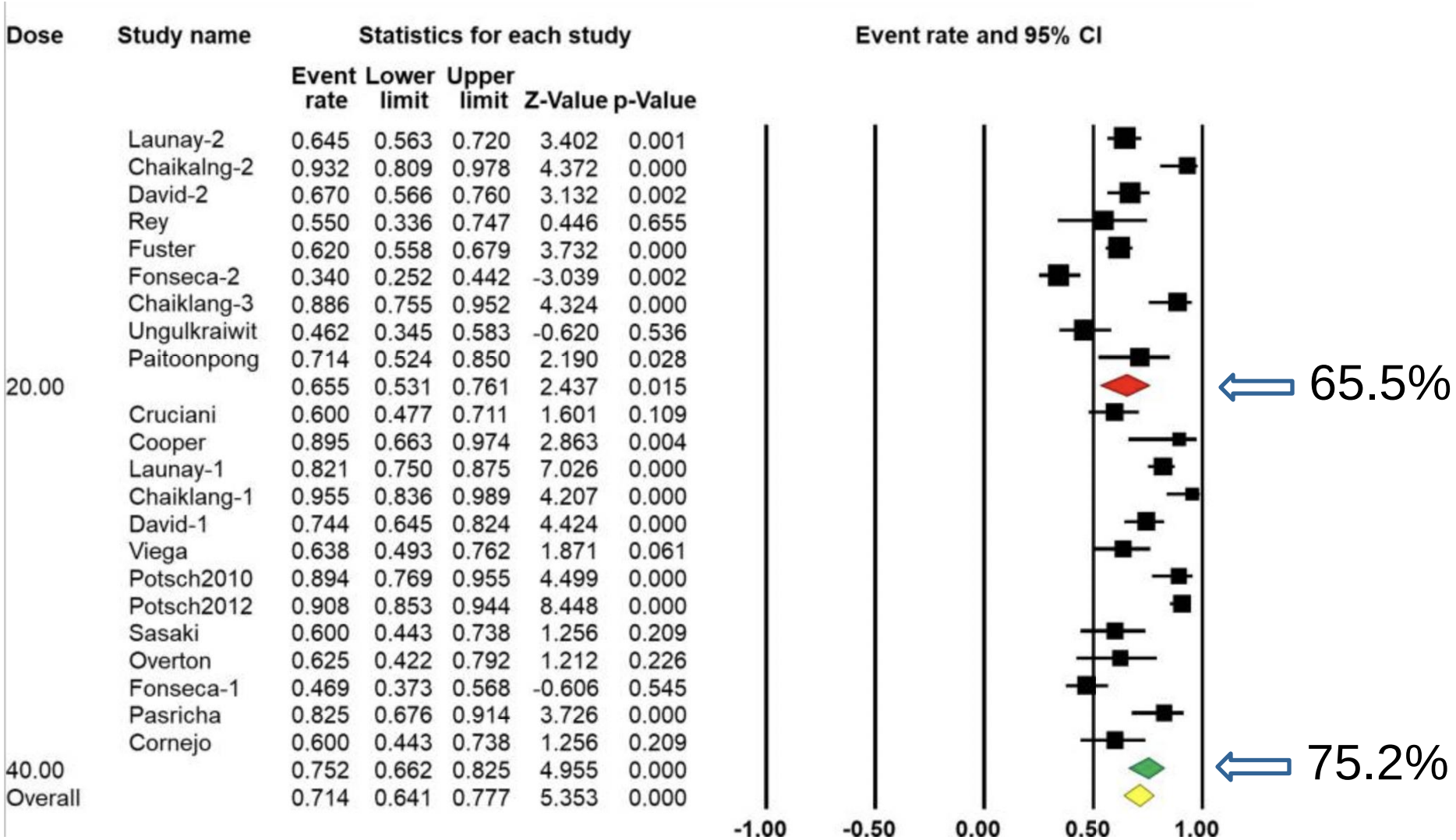
Heplisav-B vs. Engerix-B in Adults 18-70 Years of Age
Differences in Rates by Subgroup



Source: Jackson S, et al. Vaccine. 2018:36:668-74.

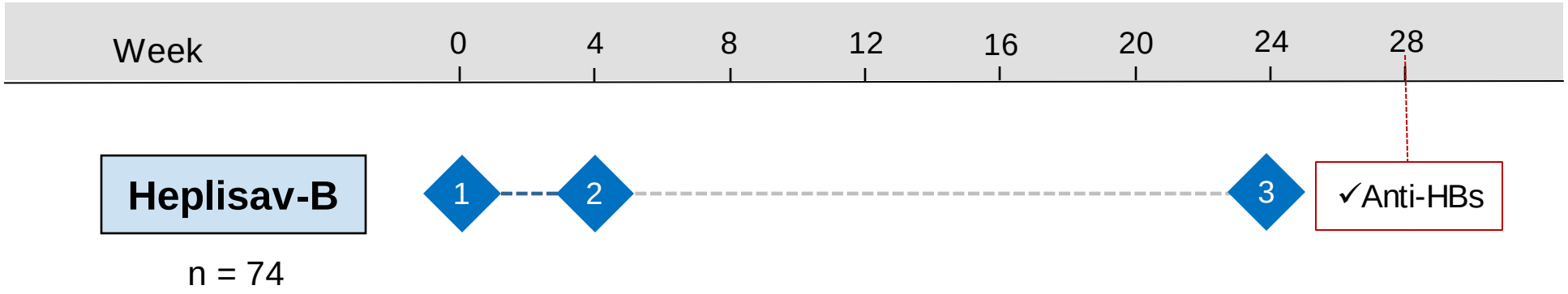
Suboptimal Seroprotective Responses with Recombinant HBV vaccine in People with HIV



Dose	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
	Launay-2	0.645	0.563	0.720	3.402	0.001
	Chaikalng-2	0.932	0.809	0.978	4.372	0.000
	David-2	0.670	0.566	0.760	3.132	0.002
	Rey	0.550	0.336	0.747	0.446	0.655
	Fuster	0.620	0.558	0.679	3.732	0.000
	Fonseca-2	0.340	0.252	0.442	-3.039	0.002
	Chaiklang-3	0.886	0.755	0.952	4.324	0.000
	Ungulkraiwit	0.462	0.345	0.583	-0.620	0.536
	Paitoonpong	0.714	0.524	0.850	2.190	0.028
20.00		0.655	0.531	0.761	2.437	0.015
	Cruciani	0.600	0.477	0.711	1.601	0.109
	Cooper	0.895	0.663	0.974	2.863	0.004
	Launay-1	0.821	0.750	0.875	7.026	0.000
	Chaiklang-1	0.955	0.836	0.989	4.207	0.000
	David-1	0.744	0.645	0.824	4.424	0.000
	Viega	0.638	0.493	0.762	1.871	0.061
	Potsch2010	0.894	0.769	0.955	4.499	0.000
	Potsch2012	0.908	0.853	0.944	8.448	0.000
	Sasaki	0.600	0.443	0.738	1.256	0.209
	Overton	0.625	0.422	0.792	1.212	0.226
	Fonseca-1	0.469	0.373	0.568	-0.606	0.545
	Pasricha	0.825	0.676	0.914	3.726	0.000
	Cornejo	0.600	0.443	0.738	1.256	0.209
40.00		0.752	0.662	0.825	4.955	0.000
Overall		0.714	0.641	0.777	5.353	0.000

Source: Tian Y et al, *Front Immunol*. 2021;12:745541.

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



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

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

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

Baseline Characteristic	Heplisav-B (n = 74)
Age, median (IQR), years	47 (40, 51)
Male at birth, n (%)	34 (46)
Race, n (%) Asian Black White Other	 49 (66) 12 (16) 11 (15) 2 (3)
Hispanic or Latino, n (%)	11 (15)
Smoker, n (%)	9 (12)
CD4 cell count, median (IQR), cells/mm^3	625 (473, 829)
HIV RNA suppression, n (%)	71 (96)

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

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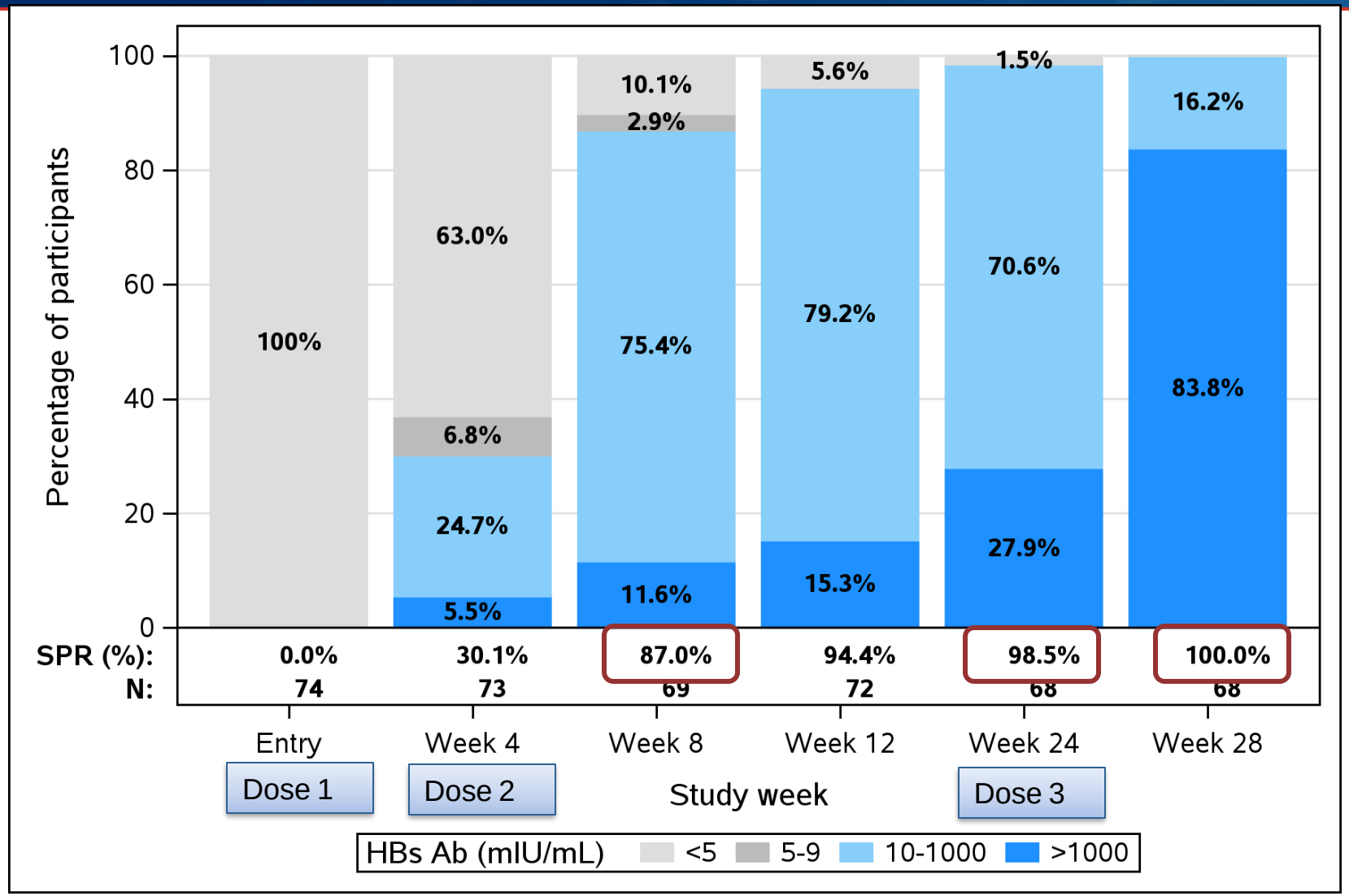
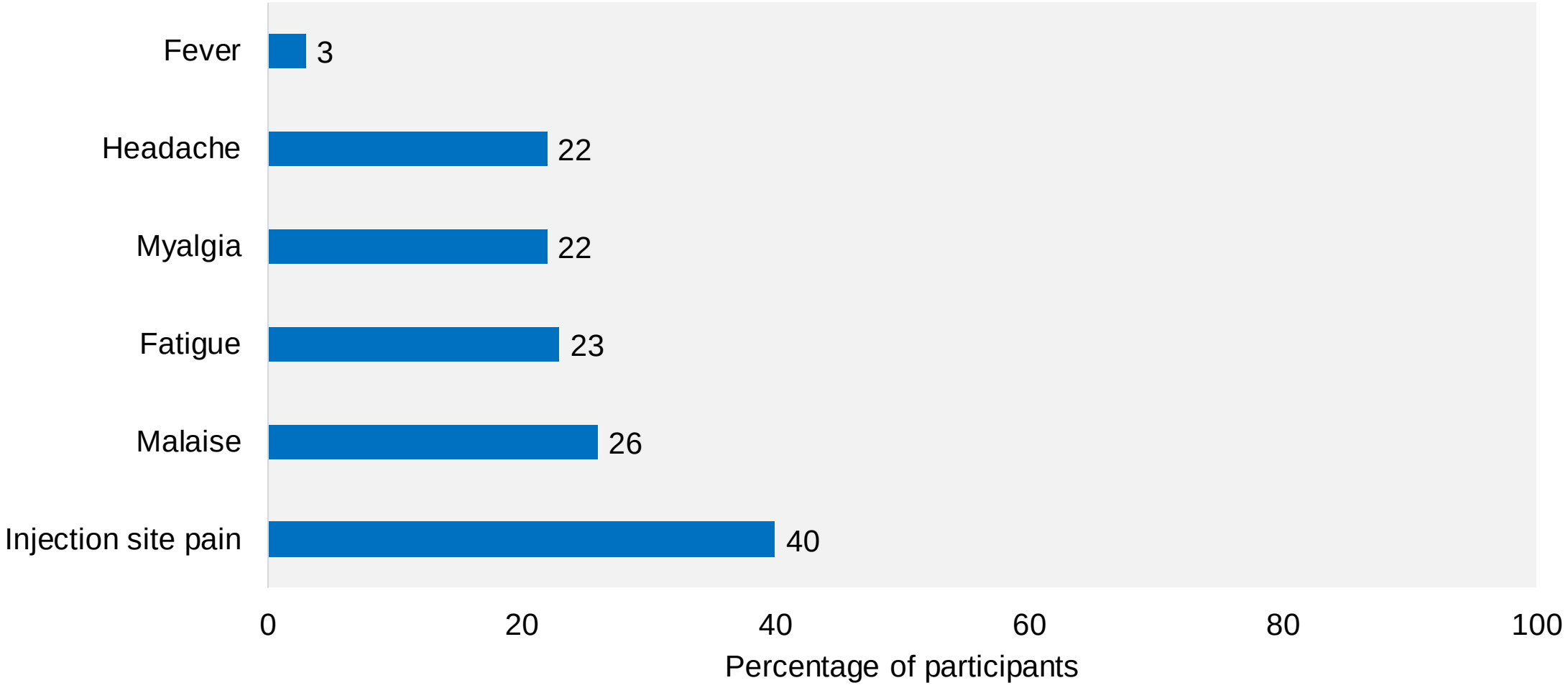
Heplisav-B: Vaccine-Naïve Adults with HIV (Group B) Bee-HIVe Trial (ACTG 5379): Seroprotective Response by Study Week



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

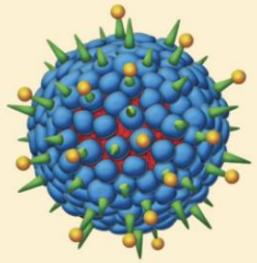
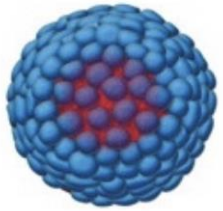
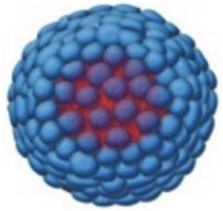
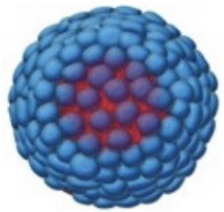
Heplisav-B: Vaccine-Naïve Adults with HIV (Group B) Bee-HIVe Trial (ACTG 5379): Adverse Events



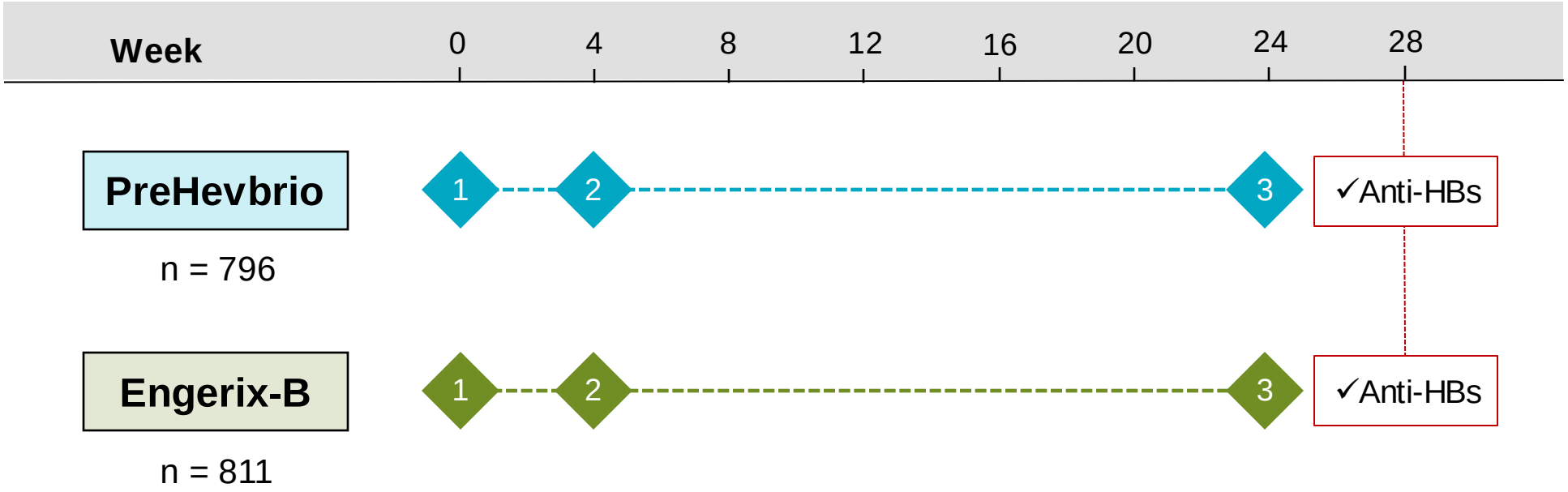
Source: Marks et al, IDWeek 2022, Washington DC. Abstract LB749.

Tri-antigenic HBV vaccine (*PreHevbrio*)

PreHevbrio – 3 Hepatitis B Surface Antigens

	PreHevbrio™ 	Engerix-B®[1] *Hepatitis B Vaccine (Recombinant)* 	Recombivax HB® *Hepatitis B Vaccine (Recombinant)* 	Heplisav-B® *Hepatitis B Vaccine (Recombinant), Adjuvanted* 
Viral antigens mimicked:				
S Antigen 	✓	✓	✓	✓
Pre-S2 Antigen 	✓			
Pre-S1 Antigen 	✓			
Derivation:	Mammalian (CHO) Cell	rDNA yeast	rDNA yeast	rDNA yeast
Adjuvant:	500µg Aluminum hydroxide	500µg Aluminum hydroxide	500µg Aluminum hydroxide	3000µg CpG 1018
Dose of HBs Antigens:	10µg	20µg	10µg or 40µg (HD)	20µg

PreHevbrio vs. Engerix-B Vaccine in Adults
PROTECT Trial: Design



Participants

HBV naïve adults (≥18 years) in stable health

Exclusions: HBV, HIV, pregnancy or lactation

Vaccine Dosing

PreHevbrio: 1.0 mL dose of 10 µg HBs antigens

Engerix-B: 1 mL dose of 20 µg recombinant HBsAg

Source: Vesikari T, et al. Lancet Infect Dis. 2021;21:1271-81.

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PreHevbrio vs. Engerix-B Vaccine in Adults Baseline Characteristics

Baseline Characteristic	**PreHevbrio** (n = 796)	**Engerix-B** (n = 811)
Age, mean (range), years	56.6 (18-86)	56.6 (18-90)
Male, n (%)	315 (39.6)	303 (37.4)
Race, n (%) White Black/African American Asian, Pacific Islander, AI/AN	 715 (89.8) 66 (8.3) 15 (1.8)	 730 (90.0) 65 (8.0) 16 (2.0)
Current smoker, n (%)	104 (13.1)	113 (13.9)
Type 2 diabetes, n (%)	60 (7.5)	65 (8.0)
Country or region USA Canada Europe	 338 (42.5) 126 (15.8) 332 (41.7)	 342 (42.2) 133 (16.4) 336 (41.4)

Source: Vesikari T, et al. Lancet Infect Dis. 2021;21:1271-81.

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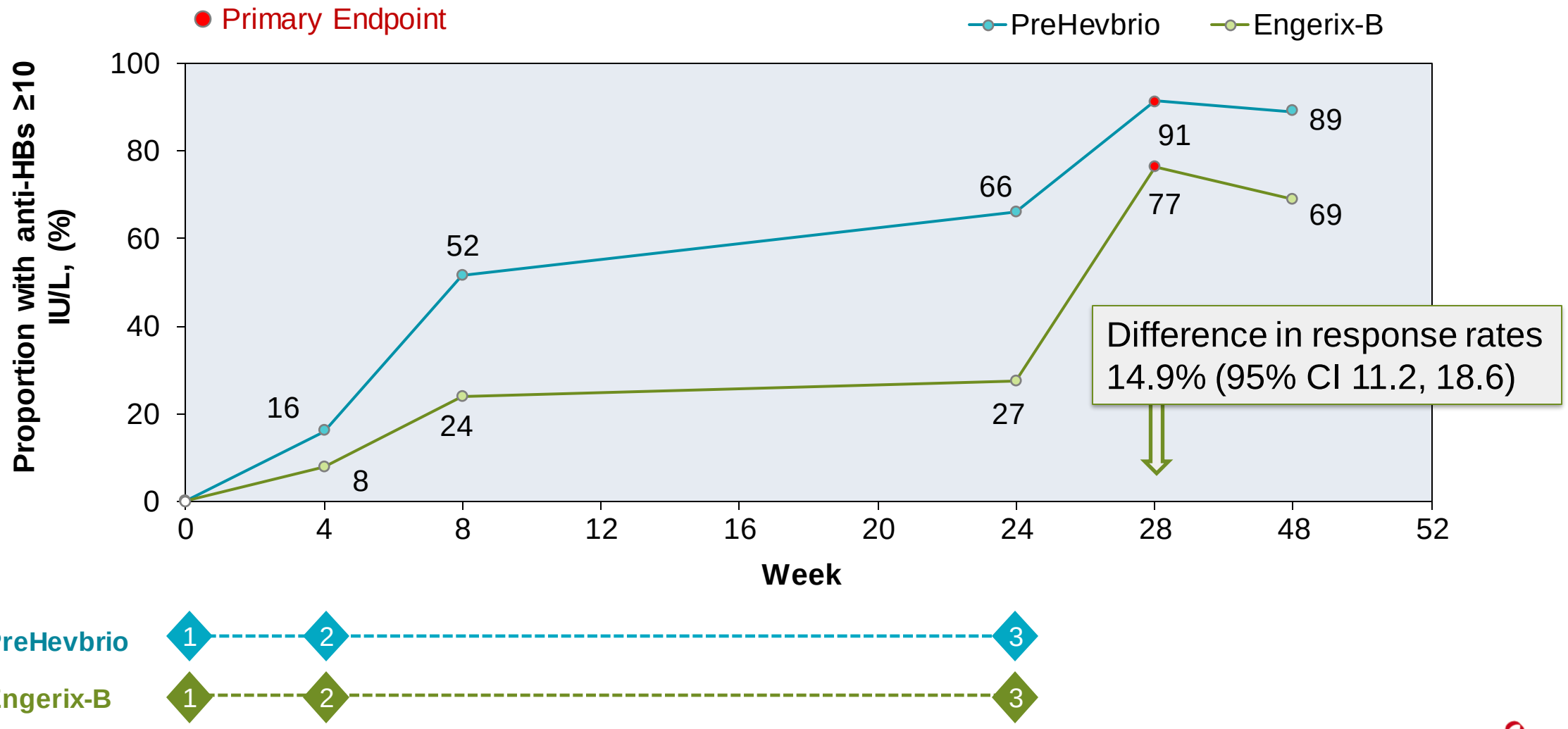
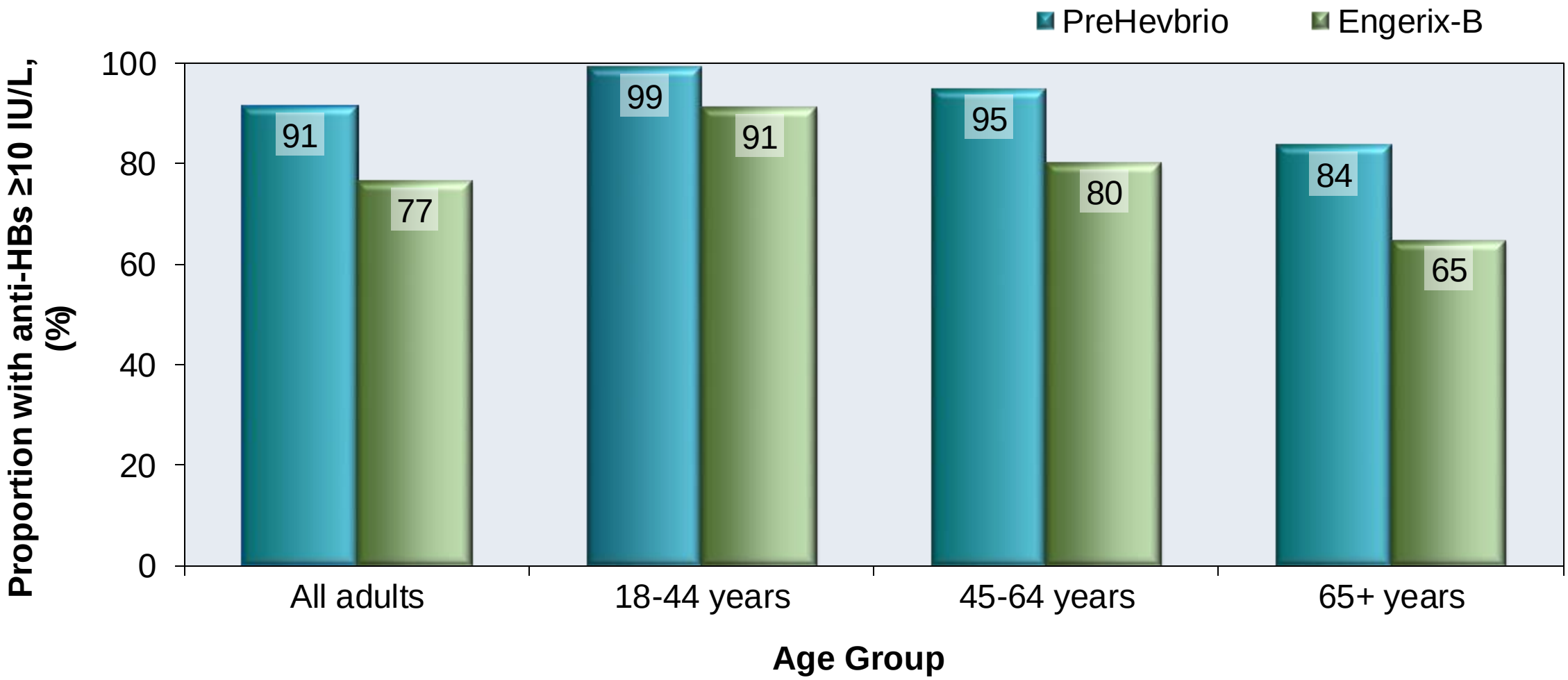
PreHevbrio vs. Engerix-B Vaccine in Adults Seroprotection Rates by Study Week



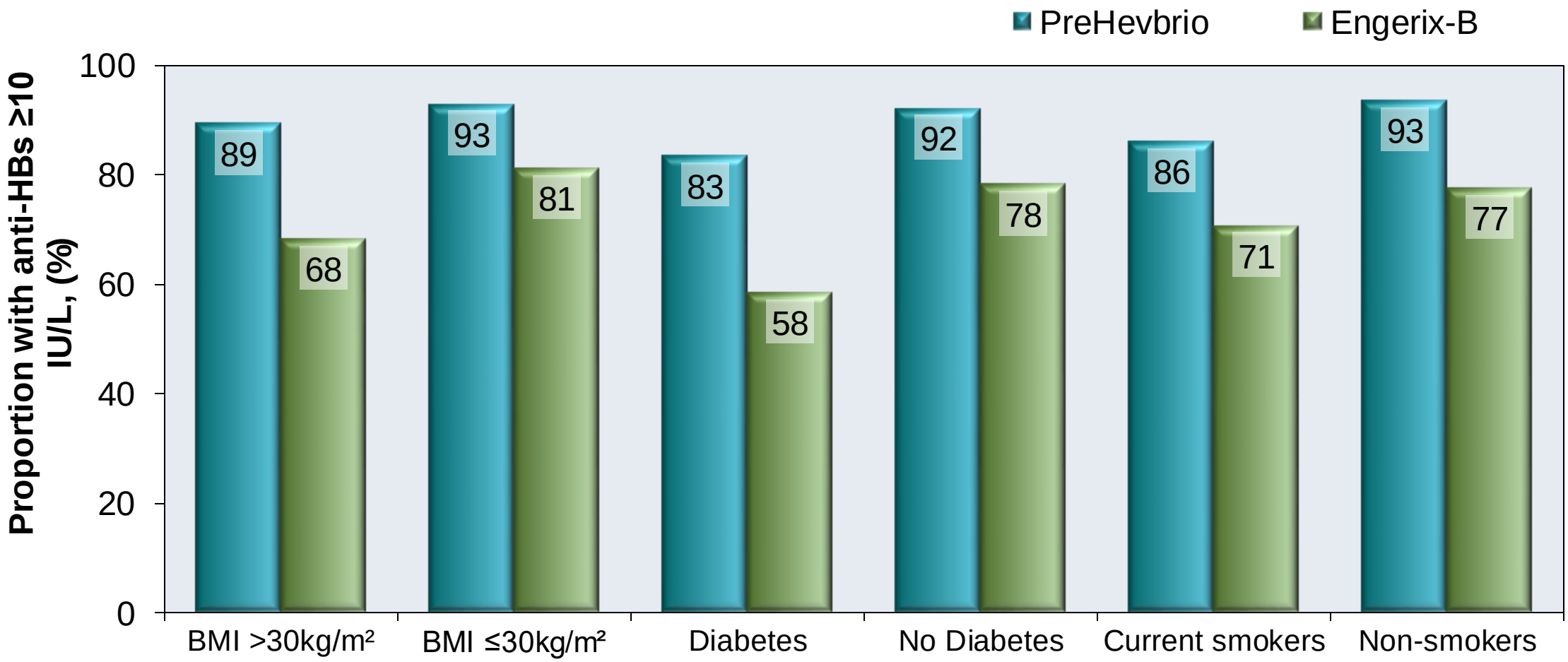
Source: Vesikari T, et al. Lancet Infect Dis. 2021;21:1271-81.

PreHevbrio vs. Engerix-B Vaccine in Adults Seroprotection Rates, by Age Group



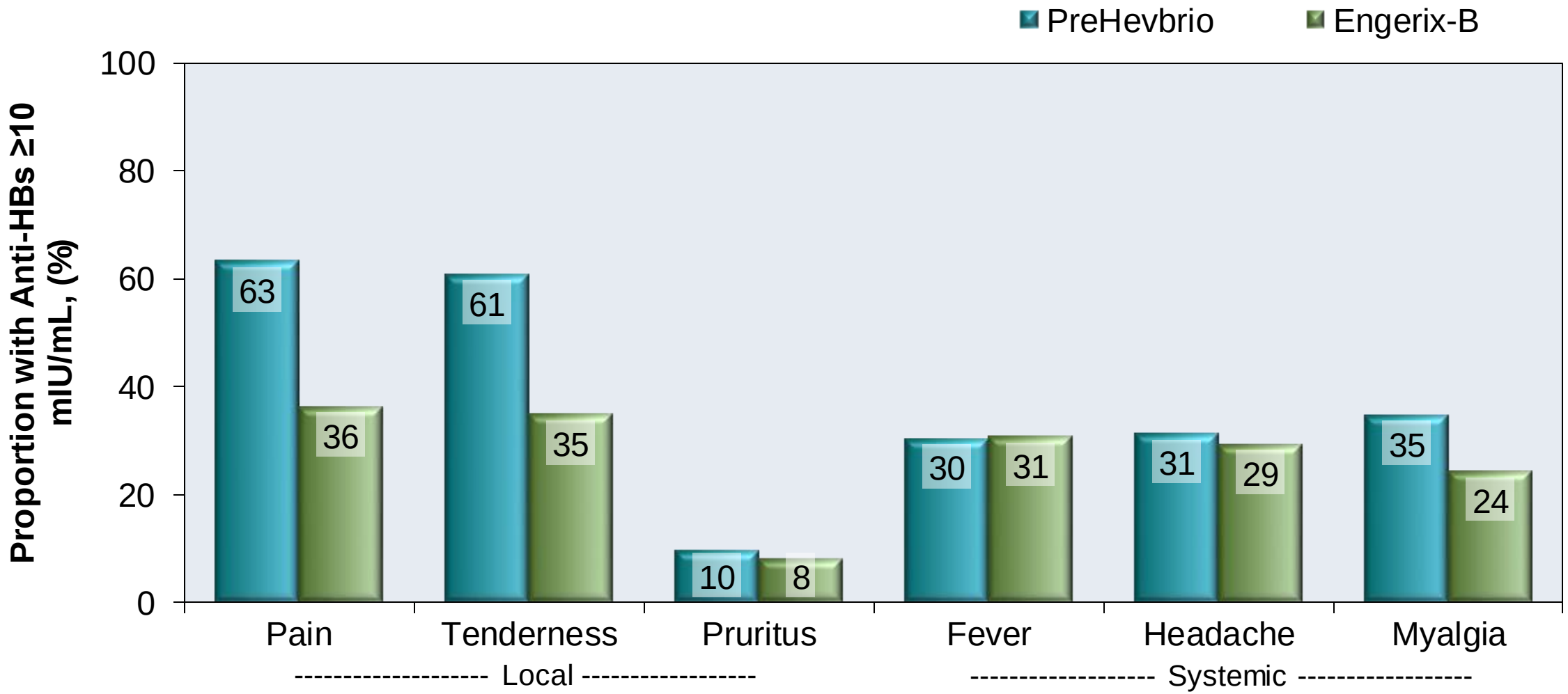
Source: Vesikari T, et al. Lancet Infect Dis. 2021;21:1271-81.

PreHevbrio vs. Engerix-B Vaccine in Adults Seroprotection Rates, by BMI, Diabetes, and Smoking



Source: Vesikari T, et al. Lancet Infect Dis. 2021;21:1271-81.

PreHevbrio vs. Engerix-B Vaccine in Adults
Safety: Adverse Events



Source: Vesikari T, et al. Lancet Infect Dis. 2021;21:1271-81.

Case 1 part 2: On HBV PrEP?

25-year-old man with HIV infection, CD4 count of 190 cells/mm^3 and virally suppressed in tenofovir DF-emtricitabine and dolutegravir is here for routine care. Has had multiple male partners in the past 2 months and would like STI screening. On review of labs, you note that his anti-HBc, anti-HBs and hepatitis B surface Ag are all negative.

What would you do next?

A. Wait for CD4 >200 cells/mm^3 before starting HBV immunization series.

B. Immunize with double-dose recombinant hepatitis B vaccine (*Engerix*).

C. Don't bother to immunize for HBV since he's currently on tenofovir.

D. Immunize with CpG-adjuvanted HBV vaccine (*Heplisav-B*).

E. Immunize with 3-antigen HBV vaccine (*PreHevbrio*).

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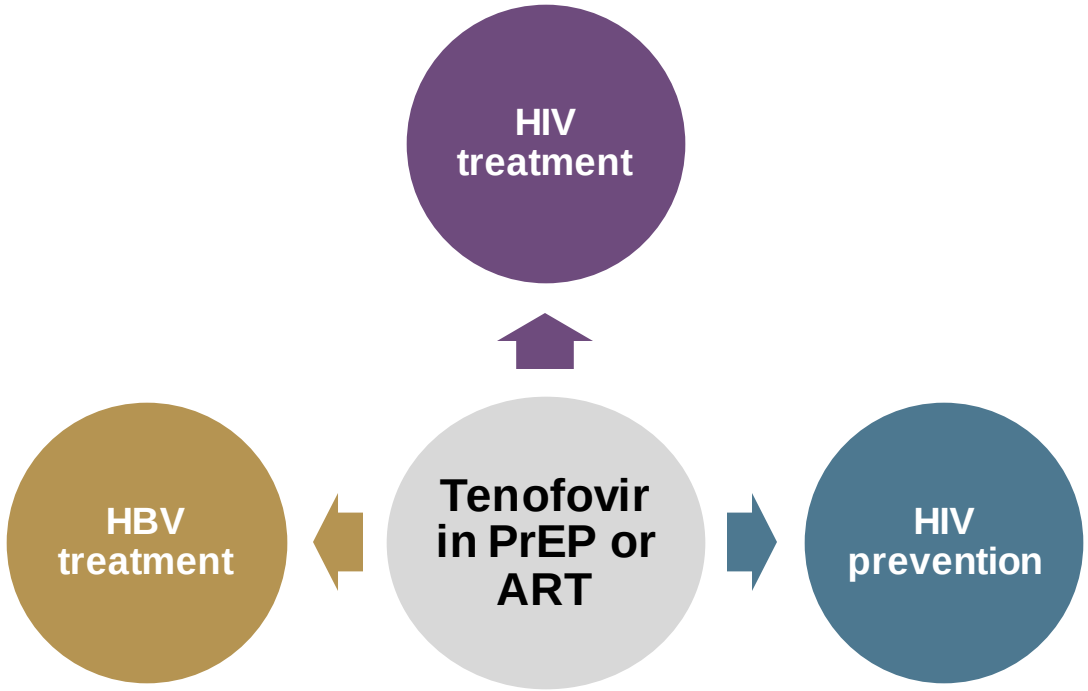
Tenofovir as Chemoprophylaxis against HBV



Tenofovir for HBV Prevention

Author	**Population Setting** All HBV susceptible at baseline w/ f/up serologic testing.	**Effect** (pyr = person-years)
Gatanaga et al (2013)	N=354 HIV+ MSM in a clinic, Japan.	No ART: 6.7/100 pyr 3TC or TDF in ART: 0.7/100 pyrs
Heuft et al (2014)	N=381 HIV+ MSM in a hospital, Netherlands.	HBV incidence: 1.1%. No HBV-active ART: 2.85/100 pyr 3TC in ART: 1.36/100 pyr TDF in ART: 0.14/100 pyr
Falade-Nwulia et al (2015)	N=2375 MSM in Multicenter AIDS Cohort Study (US)	HBV incidence: 0.96 per 100 pyr Suppressed on ART: **IRR 0.1**
Shilaih et al (2016)	N=1716 HIV+ (MSM, heterosexual, PWID) in Swiss HIV cohort. *Included those with isolated core Ab*	HBV incidence: 1.6% TDF + 3TC or FTC in ART: **HR 0.4**
Mizushima et al (2020)	N=591 MSM in sexual health clinics, Japan. HBV susceptible, 25% on PrEP	HBV incidence 3.6%. One event in PrEP; 14 in non-PrEP. HR 0.11 (adjusted **HR 0.12**)

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ORIGINAL ARTICLE

Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load

Calvin Q. Pan, M.D., Zhongping Duan, M.D., Erhei Dai, M.D., Shuqin Zhang, M.D., Guorong Han, M.D., Yuming Wang, M.D., Huaihong Zhang, M.D., Huaibin Zou, M.D., Baoshen Zhu, M.D., Wenjing Zhao, M.D., and Hongxiu Jiang, M.D., for the China Study Group for the Mother-to-Child Transmission of Hepatitis B*

ABSTRACT

BACKGROUND

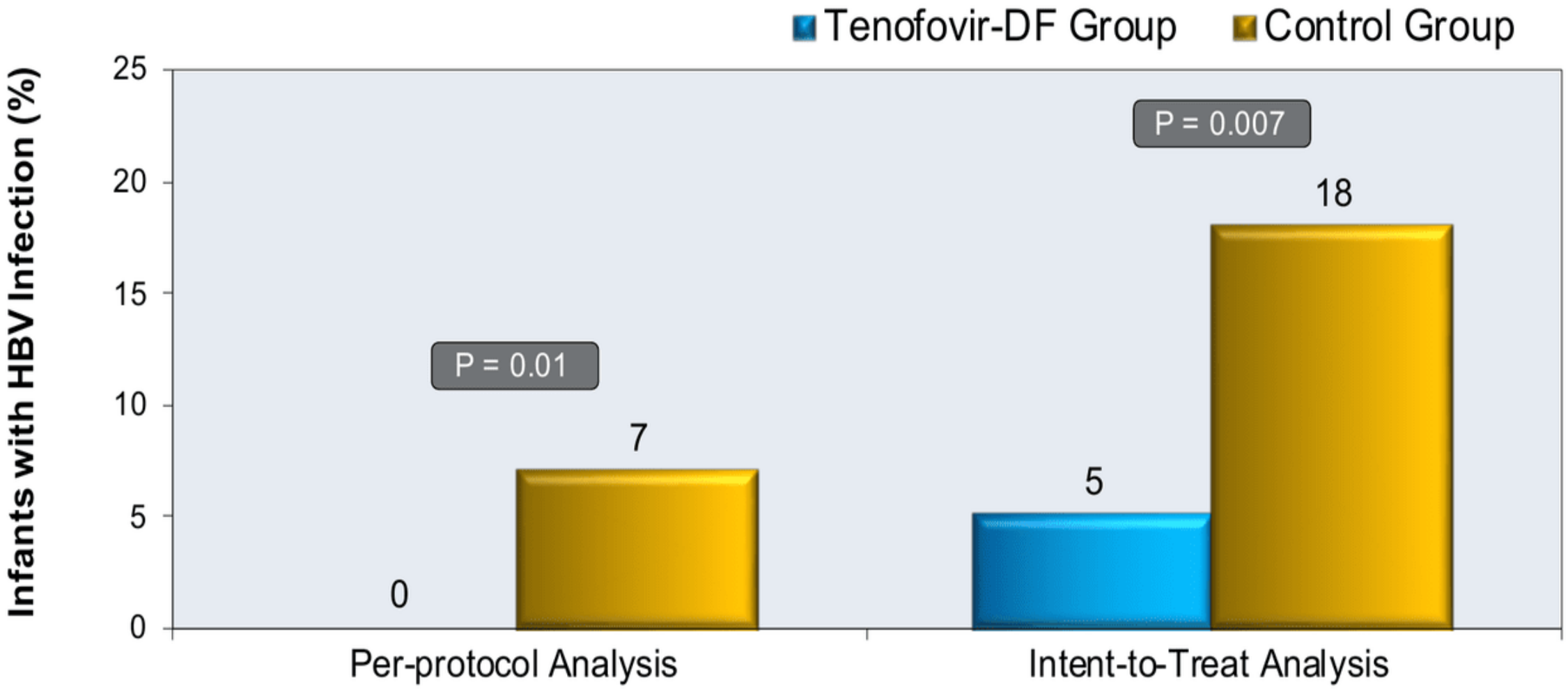
Few data are available regarding the use of tenofovir disoproxil fumarate (TDF) during pregnancy for the prevention of mother-to-child transmission of hepatitis B virus (HBV).

METHODS

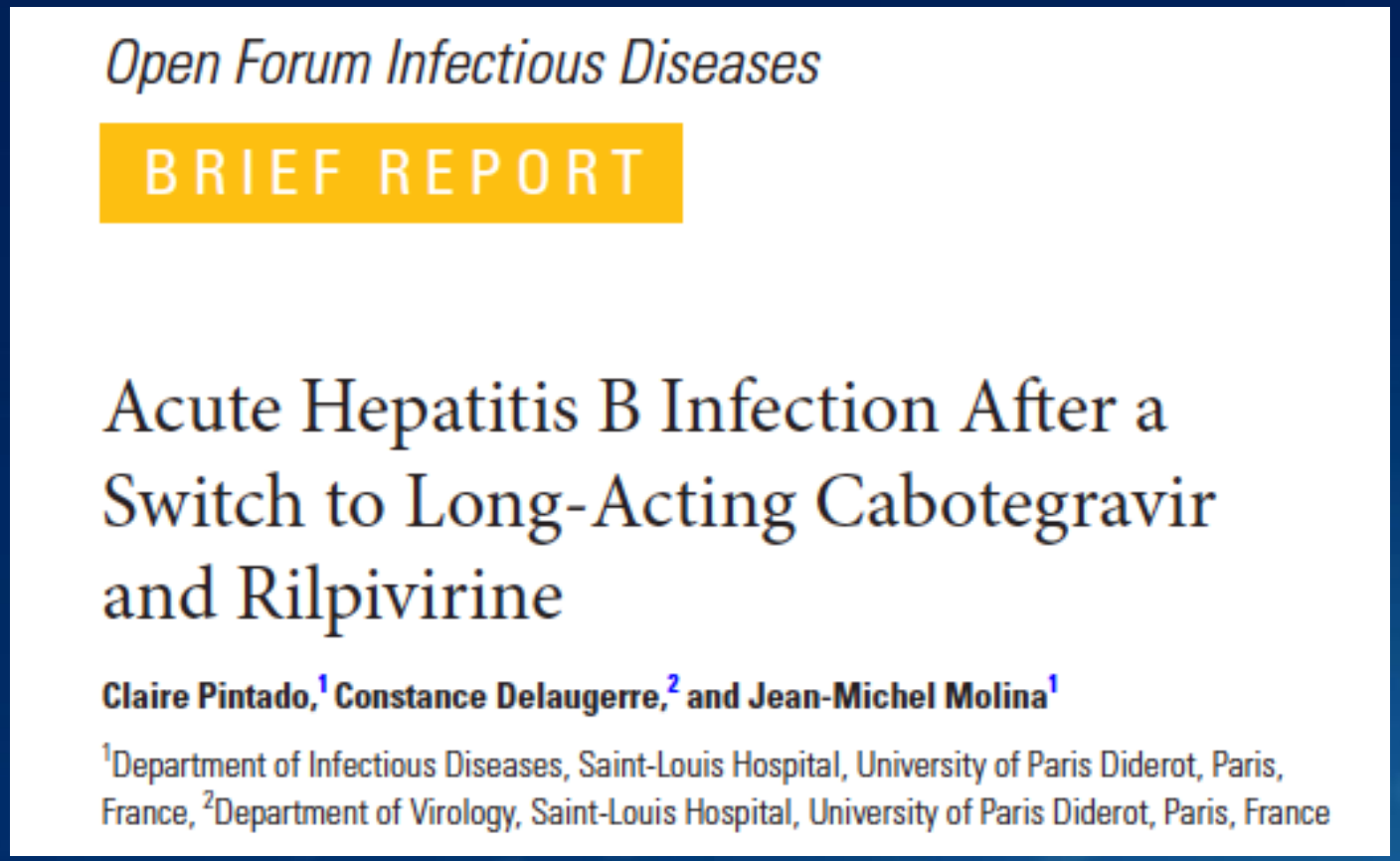
In this trial, we included 200 mothers who were positive for hepatitis B e antigen (HBeAg) and who had an HBV DNA level higher than 200,000 IU per milliliter. Participants were randomly assigned, in a 1:1 ratio, to receive usual care without antiviral therapy or to receive TDF (at an oral dose of 300 mg per day) from 30 to 32 weeks of gestation until postpartum week 4; the participants were followed until postpartum week 28. All the infants received immunoprophylaxis. The primary outcomes were the rates of mother-to-child transmission and birth defects. The secondary outcomes were the safety of TDF, the percentage of mothers with an HBV DNA level of less than 200,000 IU per milliliter at delivery, and loss or seroconversion of HBeAg or hepatitis B surface antigen at postpartum week 28.

N Engl J Med 2016;374:2324-34.
DOI: 10.1056/NEJMoa1508660

Tenofovir for Perinatal HBV Prevention



Source: Pan et al, N Engl J Med. 2016;374:2324-34.



Open Forum Infectious Diseases

BRIEF REPORT

Acute Hepatitis B Infection After a Switch to Long-Acting Cabotegravir and Rilpivirine

Claire Pintado,[1] Constance Delaugerre,[2] and Jean-Michel Molina[1]

[1]Department of Infectious Diseases, Saint-Louis Hospital, University of Paris Diderot, Paris, France, [2]Department of Virology, Saint-Louis Hospital, University of Paris Diderot, Paris, France

- Enrolled in FLAIR trial of cabotegravir + rilpivirine monthly injections
- Found to have acquired **acute HBV** – ALT peaked to 594 IU/L. HBsAg and core IgM (+). HBV DNA 229 million IU/ml.
- HBV susceptible → non-response to standard vaccine series

Pintado et al, *Open Forum Infect Dis* 2020; Sep 25;7(9):ofaa367.

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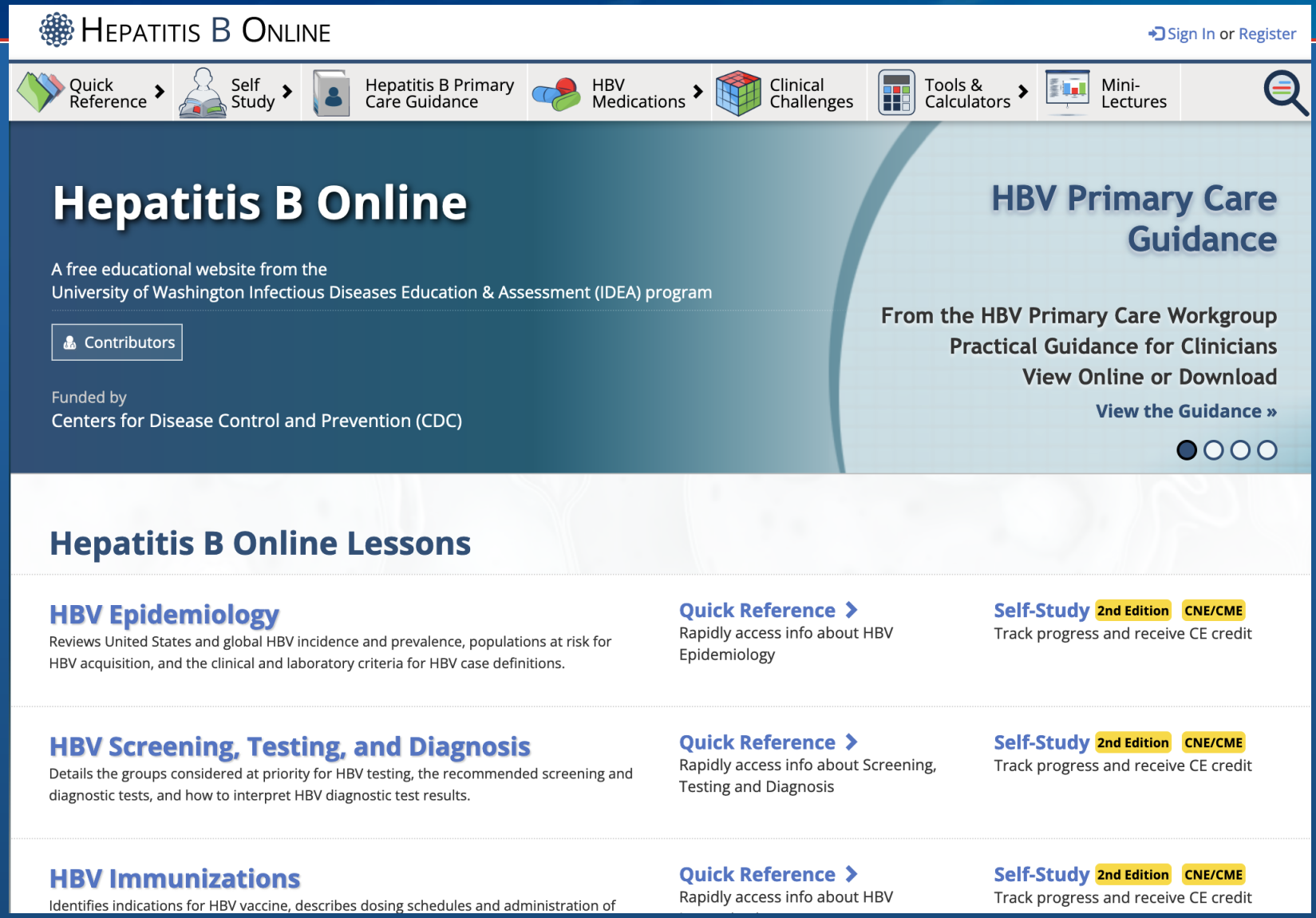
Thanks for your attention!



www.hepatitisb.uw.edu

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