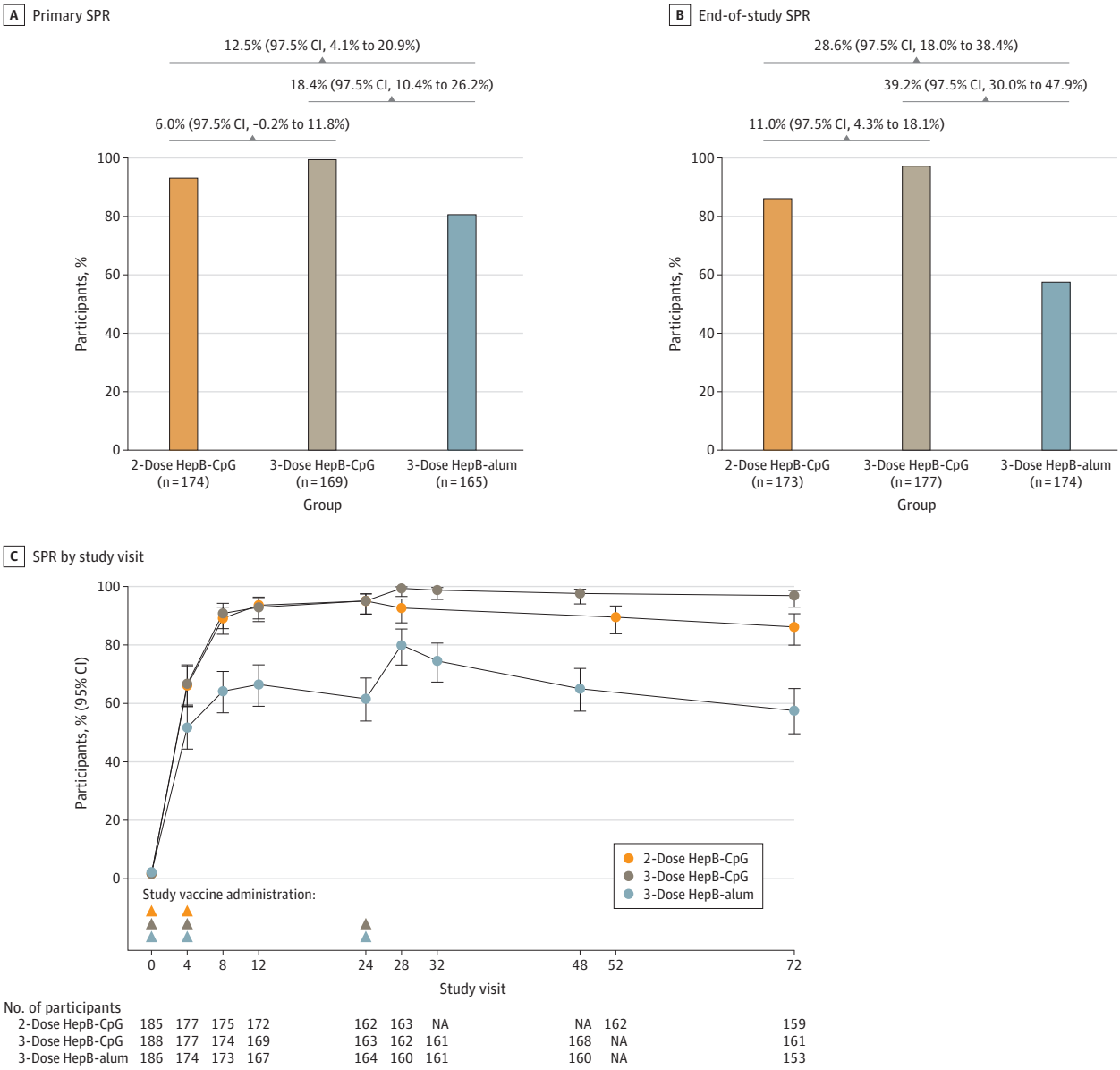
RESEARCH LETTER

HepB-CpG Vaccine in People With HIV and Prior Nonresponse to HBV Vaccine: The BEe-HIVe Trial End-of-Study Results

Hepatitis B virus (HBV) remains a leading cause of liver disease morbidity and mortality worldwide, and inadequate vaccination and waning immunity account for new HBV infections in adults.[1,2] In people with HIV with prior HBV vaccine nonresponse, the BEe-HIVe trial demonstrated that 2- and 3-dose hepatitis B vaccine with a cytosine phosphoguanine adjuvant (HepB-CpG) achieved a superior seroprotection response compared with 3-dose

Supplemental content

Figure. Seroprotection Response (SPR) by Vaccine Regimen at Study Visits



A, Primary SPR outcome was at week 12 for the 2-dose hepatitis B vaccine with a cytosine phosphoguanine adjuvant (HepB-CpG) and at week 28 for the 3-dose HepB-CpG and 3-dose hepatitis B vaccine with an aluminum hydroxide adjuvant (HepB-alum).[3] B, The end-of-study SPR outcome was at week 72. In panels A and B, the estimated SPR proportion differences between study groups with 97.5% CIs are shown above the bars. C, SPR proportions at study visits are shown, according to the protocol-specified visit windows. The visit schedules differed between the 2-dose and 3-dose groups. NA stands for not applicable.

Table. End-of-Study (EOS) Seroprotection Response (SPR) by Primary Antihepatitis B Surface (Anti-HBs) Titer Among the Participants Who Had Primary SPR Outcome[a]

	2-Dose HepB-CpG		3-Dose HepB-CpG		3-Dose HepB-alum	
	No.	EOS SPR, No. (%)	No.	EOS SPR, No. (%)	No.	EOS SPR, No. (%)
Total	154	140 (91)	163	159 (98)	128	95 (74)
By anti-HBs titer at the time of primary response, mIU/mL						
10-99	36	22 (61)	4	1 (25)	27	0
100-1000	73	73 (100)	29	28 (97)	46	40 (87)
>1000	45	45 (100)	130	130 (100)	55	55 (100)

[a] The summary is limited to participants with primary SPR outcome who had anti-HBs results available at the end of study. Primary outcome was at week 12 for 2-dose hepatitis B vaccine with a cytosine phosphoguanine adjuvant (hepB-CpG) and at week 28 for 3-dose hepB-CpG and 3-dose hepatitis B vaccine with an aluminum hydroxide adjuvant (hepB-alum).

hepatitis B vaccine with an aluminum hydroxide adjuvant (HepB-alum).[3,4] Durability of seroprotection response, 1 year or more after the vaccination series, is now reported.

Methods | The BEe-HIVe study evaluated immunogenicity of HepB-CpG in people with HIV taking antiretroviral therapy with CD4 count of 100 cells/mm^3 or greater and HIV-1 RNA less than 1000 copies/mL. The trial protocol and all amendments were reviewed and approved by independent institutional review boards and ethics committees. All participants provided written informed consent. Adults with HIV and prior nonresponse to HBV vaccine were randomized 1:1:1 to either 2 doses of HepB-CpG intramuscularly (20 µg of recombinant hepatitis B surface antigen [HBsAg] and 3000 µg of CpG 1018 adjuvant) at weeks 0 and 4; 3 doses of HepB-CpG intramuscularly at weeks 0, 4, and 24; or 3 doses of HepB-alum intramuscularly (20 µg of recombinant HBsAg) at weeks 0, 4, and 24. The primary seroprotection response, defined as antibody to HBsAg (anti-HBs) level of 10 mIU/mL or greater, at week 12 for the 2-dose regimen (8 weeks after dose 2) and week 28 for the 3-dose regimens (4 weeks after dose 3) was reported previously.[3,4] The end-of-study seroprotection response at week 72 (48 weeks after 3 doses, 68 weeks after 2 doses) reported here was a prespecified secondary outcome, and the estimation of proportion differences followed the primary response analysis approach (2-sided 97.5% Newcombe CI, stratified by sex at birth and diabetes status).[3] End-of-study seroprotection response was also summarized by the anti-HBs titer level at the time of primary response. All analyses were conducted using SAS software (version 9.4 for Linux; SAS Institute Inc).

Results | A total of 561 participants with HIV and prior vaccine nonresponse were enrolled at 41 sites in 10 countries; 96% received all study vaccine doses and 95% completed study follow-up.

At the end of study (72 weeks), 86.1% who received 2 doses of HepB-CpG vaccine (n = 173), 97.2% who received 3 doses of HepB-CpG vaccine (n = 177), and 57.5% who received 3 doses of HepB-alum (n = 174) had seroprotection response. The **Figure** illustrates seroprotection response proportion difference estimates of primary[3] and end-of-study responses.

The **Table** shows the relationship between the primary anti-HBs titer and the end-of-study seroprotection response. Among those with primary anti-HBs level greater than 1000 mIU/mL, 100% in all groups had seroprotection response at study end. Nearly all in the 3-dose HepB-CpG group had primary anti-HBs levels greater than 1000 mIU/mL. In contrast, among those with anti-HBs levels less than 100 mIU/mL at primary response, 0% in the 3-dose HepB-alum group and 61% in the 2-dose HepB-CpG group had end-of-study seroprotection responses.

Reactogenicity was reported previously.[3] No new safety issues were identified. Two unrelated deaths occurred (tuberculosis and cardiac arrest).

Discussion | In people with HIV, HepB-CpG vaccine achieved durable seroprotection in people with prior vaccine nonresponse. Higher end-of-study seroprotection was achieved with HepB-CpG compared with HepB-alum, and 3 doses of HepB-CpG compared with 2 doses. This is consistent with the previously reported primary response (4 or 8 weeks post vaccination) and strengthens the recommendation to use HepB-CpG in people with HIV. Similarly, HepB-CpG has achieved high levels of seroprotection in health care workers with prior vaccine nonresponse.[5]

Primary response titer of 100 mIU/mL or greater led to high end-of-study seroprotection responses; furthermore, titer greater than 1000 mIU/mL, most common with 3 doses of HepB-CpG, resulted in 100% seroprotection responses at the end of study in all groups. Current guidelines recommend checking for seroprotection response 4 weeks after final dose and then to consider annual testing, particularly if a person has ongoing risk factors for acquiring HBV and is not receiving tenofovir.[6] Given the increasing use of antiretroviral therapy without HBV activity, the use of 3 doses of vaccine to achieve a higher anti-HBs titer and improve the durability of seroprotection may outweigh the cost or convenience benefits of 2 doses. A planned cost-effectiveness analysis will provide further insight into these decisions.

Kristen M. Marks, MD
Minhee Kang, PhD
Triin Umbleja, MSc
Andrea Cox, MD, PhD
Karen J. Vigil, MD
Anchalee Avihingsanon, MD, PhD
Patcharaphan Sugandhavesa, MD
Leolin Katsidzira, MBChB, DPhil
Josphat Kosgei, MBChB
Hugo Perazzo, MD, PhD

Jennifer Price, MD, PhD
Stephanie Caruso, MBA
Kevin Knowles, PhD
Beverly L. Alston-Smith, MD
Parita Rathod, BS
Kenneth E. Sherman, MD, PhD
for the ACTG 5379 (BEe-HIVe) Study Team

Author Affiliations: Weill Cornell Medicine, New York, New York (Marks); Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Kang, Umbleja); The Johns Hopkins University School of Medicine, Baltimore, Maryland (Cox); University of Texas at Houston (Vigil); HIV-NAT, Thai Red Cross AIDS Research Centre and CE in Tuberculosis, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (Avihingsanon); Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand (Sugandhavesa); University of Zimbabwe, Harare, Zimbabwe (Katsidzira); Walter Reed Project–Kericho, Kericho, Kenya (Kosgei); Oswaldo Cruz Foundation–Fiocruz, Rio de Janeiro, Brazil (Perazzo); University of California, San Francisco (Price); Frontier Science & Technology Research Foundation Inc, Amherst, New York (Caruso, Knowles); National Institute of Allergy and Infectious Diseases, Rockville, Maryland (Alston-Smith); DLH Corporation, Bethesda, Maryland (Rathod); Massachusetts General Hospital, Boston (Sherman); University of Cincinnati College of Medicine, Cincinnati, Ohio (Sherman).

Accepted for Publication: May 23, 2025.

Published Online: July 2, 2025. doi:10.1001/jama.2025.9894

Corresponding Author: Kristen Marks, MD, Weill Cornell Medicine, 53 W 23rd St, 6th Floor, New York, NY 10011 (markskr@med.cornell.edu).

Author Contributions: Dr Marks had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Marks, Kang, Umbleja, Cox, Alston-Smith, Sherman.
Acquisition, analysis, or interpretation of data: Marks, Kang, Umbleja, Cox, Vigil, Avihingsanon, Katsidzira, Sugandhavesa, Kosgei, Perazzo, Price, Caruso, Knowles, Rathod, Sherman.
Drafting of the manuscript: Marks, Kang, Sherman.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Kang, Umbleja.
Obtained funding: Marks, Cox, Sherman.
Administrative, technical, or material support: Cox, Perazzo, Caruso, Knowles, Rathod.
Supervision: Marks, Kang, Vigil.
Other—conducted the study at our site: Avihingsanon.
Other—clinical oversight as representative of the regulatory sponsor: Alston-Smith.
Other—data management and QC: Knowles.

Conflict of Interest Disclosures: Dr Marks reported grants from the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) during the conduct of the study; grants from Gilead Sciences and personal fees from Gilead Sciences (expert testimony), Immorna (data and safety monitoring board [DSMB]), and Novo Nordisk (DSMB) outside the submitted work. Dr Kang reported grants from NIAID/NIH during the conduct of the study. Dr Umbleja reported grants from NIH/NIAID to institution (UM1 AI068634) during the conduct of the study; grants from NIH/National Heart, Lung, and Blood Institute to institution (U01 HL123339) and grants from NIH/NIA to institution (R01 AG054366) outside the submitted work. Dr Vigil reported grants from NIH during the conduct of the study; personal fees from Gilead Sciences and ViiV and grants from Theratechnologies outside the submitted work. Dr Avihingsanon reported grants from Gilead Sciences, ViiV/GSK (paid to institution), Roche (paid to institution), Merck Sharp & Dohme (paid to institution), and Janssen Research & Development (paid to institution); transportation costs to attend meetings/conferences from Gilead Sciences; and nonfinancial support from Strategic and Technical Advisory group to the World Health Organization for HIV/hepatitis/STI, Thai AIDS society committee, and Thailand National ART, TB, HIV, and Hepatitis program committee during the conduct of the study. Dr Perazzo reported grants from CNPq, FAPERJ, and Fiotec INOVA FIOCRUZ outside the submitted work. Dr Price reported grants from Gilead Sciences, AbbVie, VIR, Cepheid, and Genentech outside the submitted work. Dr Knowles reported grants from NIH (Frontier Science Foundation receives grant funding from the NIH) during the conduct of the study. Dr Sherman reported grants from NIH/NIAID/Advancing Clinical Therapeutics Globally (ACTG) during the conduct of the study; grants from AbbVie, Gilead, Helio, Intercept, and Zydus and personal fees from MedPace, Pliant, Horizon/Amgen, CinRx, and UpToDate outside the submitted work. No other disclosures were reported.

Funding/Support: Research reported in this publication was supported by the NIAID of the NIH under ACTG grant numbers UM1 AI068634, UM1 AI068636, and UM1 AI106701. Additional funding support and study product were provided by Dynavax Technologies.

Role of the Funder/Sponsor: The NIH (Division of AIDS [DAIDS]) contributed to the design, collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dynavax contributed only to the design of the study.

Group Information: The ACTG 5379 (BEe-HIVe) Study Team members are listed in Supplement 1.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We thank people with HIV who graciously participate in research studies, especially the ACTG A5379 participants. We also acknowledge the ACTG leadership, the Hepatitis Transformative Science Group of the ACTG, and the Statistical and Data Management Center of the ACTG for their continued support and guidance. We also acknowledge the contributions of all members of the ACTG A5379 team past and present including Oladapo Alli, PharmD (DAIDS, NIH), Ceora Beijer, BS (ACTG Lab Center at University of California, Los Angeles [UCLA]), Shawn Chiambah, PhD (DAIDS, NIH), Lillian Collins, MPH (FSTRF), Kim Epperson, RN (Greensboro clinical research site [CRS]), Francoise Giguel, BA (Massachusetts General Hospital CRS), Jan Kosmyna, Michael Leonard, MLI, Terence Mohammed, BS (Gaborone CRS), Leonard Sowah, MBChB, MPH (DAIDS, NIH), Christina Vernon, MPH (DLH Corp), and Sara Zabih, MSN, RN (ACTG Lab Center at UCLA).

1. World Health Organization. Global hepatitis report 2024: action for access in low- and middle-income countries. April 9, 2024. Accessed June 2, 2025. https://www.who.int/publications/i/item/9789240091672

2. Weng MK, Doshani M, Khan MA, et al. Universal hepatitis B vaccination in adults aged 19-59 years: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(13):477-483. doi:10.15585/mmwr.mm7113a1

3. Marks KM, Kang M, Umbleja T, et al; ACTG 5379 (BEe-HIVe) Study Team. HepB-CpG vs HepB-Alum vaccine in people with HIV and prior vaccine nonresponse: the BEe-HIVe randomized clinical trial. *JAMA*. 2025;333(4):295-306. doi:10.1001/jama.2024.24490

4. Hung I, Lok AS. Overcoming hepatitis B vaccine nonresponsiveness. *JAMA*. 2025;333(4):291-292. doi:10.1001/jama.2024.24028

5. Russ RK, Vandehei HM, Golovkina MI, Mogallapalli H, Caldera F, Hayney MS. Hepatitis B-CpG vaccine series for healthcare workers who are hepatitis B vaccine nonresponders. *Clin Infect Dis*. 2024;79(2):562-563. doi:10.1093/cid/ciae320

6. ClinicalInfoHIV.gov. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. Accessed March 18, 2025. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection