

# HepB-CpG Vaccine Offers Better Hepatitis B Protection for People With HIV

Effective vaccination has added importance now that more people are using antiretroviral therapy without activity against hepatitis B virus.

July 7, 2025 By [Liz Highleyman](#)

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A hepatitis B vaccine containing a more powerful immune booster offered nearly complete protection against hepatitis B virus (HBV) for people with HIV who did not respond adequately to older HBV vaccines, according to study results published in [JAMA](#). In this analysis, 97% of people who received three doses of the HepB-CpG vaccine (Heplisav-B) developed protective antibody levels, compared with just 58% of those who got a conventional vaccine.

HIV and HBV have shared transmission routes, and many people living with HIV are also at risk for [hepatitis B](#). Over time, chronic hepatitis B can lead to serious complications, including [cirrhosis](#) and [liver cancer](#). Tenofovir disoproxil fumarate (TDF; Truvada) and tenofovir alafenamide (TAF; Descovy) have dual activity against both HIV and HBV and work as hepatitis B post-exposure prophylaxis, but a growing number of people are now using antiretroviral regimens that do not include any agents with anti-HBV activity.

[Guidelines recommend](#) that people living with HIV should be vaccinated against HBV, but some—especially those with low CD4 T-cell counts—do not respond well to conventional HBV vaccines. HepB-CpG contains cytosine phosphoguanine, a TLR-9 agonist, as an adjuvant to stimulate a stronger immune response, while the older Engerix-B and Recombivax HB vaccines contain an aluminum adjuvant.

Kristen Marks, MD, of Weill Cornell Medicine, and colleagues conducted the BEe-HIVe trial (ACTG 5379; [NCT04193189](#)) to evaluate the effectiveness of the HepB-CpG vaccine in 561 people in the United States and nine other countries. The median age was 46 years, two thirds were men, 42% were Black, 35% were white and 17% were Asian. They had a CD4 count of at least 100, an HIV viral load below 1,000, no serological evidence of prior HBV infection and had not responded to prior hepatitis B vaccination.

The study participants were randomly assigned to receive two or three doses of HepB-CpG via intramuscular injection or three shots of a conventional alum vaccine at weeks 0, 4 and 24. The

primary outcome was a seroprotective response, defined as a hepatitis B surface antibody (anti-HBs) level of 10 mIU/ml or higher.

Interim results [were presented](#) at the 2024 Conference on Retroviruses and Opportunistic Infections and [published in JAMA](#) in December 2024. In that analysis, 99% of people who received three doses of HepB-CpG and 93% of those who received two doses achieved protective antibody levels at four to eight weeks after the last dose, compared with 81% of those who received a conventional HBV vaccine.

The trial's end-of study results, published this month, show that HepB-CpG led to ongoing high response rates, especially for those who received three doses. At 72 weeks, 97% of people who received three doses of HepB-CpG and 86% of those who received two doses still had protective antibody levels, compared with 58% of those in the conventional vaccine group. All vaccines were generally safe and well tolerated with no new safety issues reported.

[Federal guidelines](#) recommend that all HIV-positive people without chronic hepatitis B or existing immunity should receive HBV vaccination, and those with inadequate response to prior vaccines should be revaccinated. Two doses of Heplisav-B is the preferred regimen, with Engerix-B, Recombivax-HB and a combination hepatitis A and B vaccine (Twinrix) as alternatives. Antibody response should be assessed one to two months after the last dose.

The guidelines advise that prior nonresponders to Engerix-B or Recombivax-HB should receive two doses of Heplisav-B, with a third dose if response remains inadequate, and prior Heplisav-B nonresponders should get a third dose. However, the study authors suggested that planning on three doses from the outset might be better option.

“Given the increasing use of antiretroviral therapy without HBV activity, the use of three doses of vaccine to achieve a higher anti-HBs titer and improve the durability of seroprotection may outweigh the cost or convenience benefits of two doses,” they wrote.

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