Literature Reviews

National HIV Curriculum Podcast

The BEe-HIVe Study: Major Findings from Two Publications

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Season 2, Episode 9

This episode reviews two recent papers on the practice-changing BEe-HIVe study, which assessed efficacy of a relatively new hepatitis B vaccine (known as HepB-CpG, or trade name *Heplisav-B*) for persons with HIV, and the resulting clinical implications.

Topics:

- OIs and HIV
- HBV
- hepB vaccine
- HepB-CpG

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Disclosures
Disclosures for Brian R. Wood, MD
None

References

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Transcript

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introduction**[00:00] Introduction**

Hello everyone. I'm Dr. Brian Wood from the University of Washington in Seattle. Welcome to the *National HIV Curriculum* Podcast. This podcast is intended for health care professionals who are interested in learning more about the diagnosis, management, and prevention of HIV.

In today's episode, I'm going to review two publications, both of which have major findings from a trial called ACTG 5379, or most people refer to it as the BEe-HIVe study. Again, you'll probably hear this as the BEe-HIVe study. Now, this study included two different groups of people with HIV. One group had never previously received hep B vaccination, and the other group had received prior hep B vaccination, but had evidence of nonresponse, meaning never achieved a seroprotective response to vaccine.

I will first review the publication of efficacy data for a vaccine called HepB-CpG for vaccine-naïve individuals. Then, I will go into a review of a separate publication of results of this novel vaccine for individuals who had a history of prior hep B vaccination, but documented nonresponse. So, if you are not familiar with the abbreviation HepB-CpG, this vaccine is more commonly called by its trade name *Heplisav-B*. I will explain a bit more where the abbreviation comes from, and we'll talk a bit more about this vaccine.

background**[01:43] Background**

Why is this topic important? First, individuals with HIV are at a higher relative risk of acquiring hepatitis B infection; and second, people with HIV have relatively lower response rates to the traditional or older hep B vaccine options. So, those older, more traditional hep B vaccines, the vaccines we used in years past prior to having access to the HepB-CpG vaccine, were aluminum hydroxide adjuvant vaccines, so they're often referred to as HepB-alum vaccines, and that is how I will refer to them. The trade names for those are *Engerix-B* and *Recombivax*, so you may know those names. Again, I will call them HepB-alum vaccines. The main downside of those alum vaccines was the low seroprotective response rate. Response rates for people with HIV ranged from 20 to 70% depending on the study. And the response rates also varied significantly depending on the CD4 count and also the viral load.

So now, the studies I'm going to review in this episode really focus on efficacy and safety of a newer vaccine, again, called HepB-CpG. This newer vaccine combines recombinant Hep B surface antigen with a novel adjuvant, so a different adjuvant than the alum vaccines. This novel adjuvant is called cytosine-phosphoguanine. That's where CpG comes from. It's called CpG 1018 if you really want to get into the weeds or details. And this is a Toll-like receptor 9 agonist. It really is designed to boost the immunologic response or boost the likelihood of a seroprotective response to the vaccine. Now, this HepB-CpG vaccine is typically given as two doses, one month apart. Though the study I will talk about actually gave three doses to a lot of individuals, the three doses were given over the course of six months. And I will come back to some pros and cons, and clinical considerations for giving two doses versus giving three doses.

Now, before I dive into the studies themselves, I also want to emphasize a point that has been made in some publications and some guidelines around the world, and that is the point that seroprotective responses following hep B vaccination may wane over time, and some data suggest that a higher surface antibody response to vaccine may lead to a more lasting response. There have actually been rare cases of hep B acquisition after a person's protective surface antibody level has waned to a level that is no longer protective. So just keep those things in mind as I review some of the data, and I will come back later to some controversy over what to do clinically with that data.

So, that's the background, and with all that being said, let me turn to a review of the first publication from this really important study called BEe-HIVe.

paper-1**[05:25] Paper #1**

Marks KM, Kang M, Umbleja T, et al. Immunogenicity and safety of hepatitis B virus (HBV) vaccine with a toll-like receptor 9 agonist adjuvant in HBV vaccine-naïve people with human immunodeficiency virus. Clin Infect Dis. 2023 Aug 14;77(3):414-418. **[PubMed Abstract]**

Now, this first publication or first part of the study looked at seroprotective response rates with HepB-CpG vaccine for people with HIV who were vaccine naïve, meaning they had never previously received any type of hep B vaccine. Results from this part of the study were published in 2023 in the journal *Clinical Infectious Diseases*, and the study was led by Dr. Kristen Marks.

overview**[05:55] Overview**

Now, for this part of the study, the main inclusion criteria were age 18 to 70 years old, no evidence of past hep B infection or hep B vaccination, and participants were taking ART [antiretroviral therapy], had a CD4 count of 100 or more, and a viral load of 1,000 or less at the time of enrollment. Now, for all participants, screening hep B serologies showed non-reactive surface antigen, surface antibody, and core antibody, indicating no prior exposure to hep B and no prior vaccination for hep B. People who enrolled in the study received intramuscular HepB-CpG for three doses. These occurred at timepoint zero, then at four weeks, and then at 24 weeks. So again, I want to note the use of three doses of HepB-CpG here instead of two. In the study, a seroprotective response was defined as achieving a surface antibody level of 10 or greater.

Turning to who enrolled in the study, there were 74 participants. It was an international study. The investigators enrolled a diverse group of individuals. Actually, 73% of participants enrolled at sites outside the U.S. The median age was 47. Median CD4 count was 625, and 96% had a viral load below 60. So, really, the take-home point here is that most participants in the study had well-controlled HIV.

results**[07:38] Results**

I will just jump to the punchline, the principal finding, which I think is quite remarkable: 100% of participants completed the vaccine series, and 100% achieved a seroprotective surface antibody response four weeks after the third dose. So again, 100% showed evidence of a protective response or really success with three doses of HepB-CpG. Another really notable, I would say, remarkable finding is that 88% of participants achieved a surface antibody titer above 1,000. And again, there may be some long-term clinical benefit of achieving a higher titer, but that is controversial and not totally clear. It'd be great to have more data on that, and I'll come back to mentioning that again a bit later. But overall, the response rate to three doses of HepB-CpG was clearly much, much better than has been seen in prior years with the alum vaccine. So that is a very notable finding.

Now, digging into the details a bit more, I want to return to the question of whether three doses of HepB-CpG is necessary or whether two doses appear sufficient. The vaccine is actually approved by the FDA as a two-dose series, those two doses at week zero and week four. But the leaders of the BEe-HIVe study opted to give three doses because of the historically low response rates to hep B vaccine for people with HIV, as I previously mentioned.

But, if we dig into the results of BEe-HIVe, I really want to highlight that the vast majority of participants in the study achieved a seroprotective response before receiving the third dose. So, it was actually over 98% of participants had evidence of seroprotection after the second dose and before the third dose. So, I think this clearly suggests that the two-dose strategy is quite effective and sufficient for most people. The authors also cite that for individuals with chronic kidney disease who are on hemodialysis, the response rates to two doses of HepB-CpG were lower, as low as 64%. So certain individuals may benefit from three doses of vaccine.

In addition, there's another finding that I think is really important. Even though surface antibody titers in the study met thresholds for seroprotection after two doses, the peak antibody levels were much higher after three doses. And again, this may mean longer duration of protection, but the overall long-term clinical benefits are not yet known.

summary**[10:40] Summary**

So, bringing this all together, for the majority of vaccine-naïve individuals in my clinic, I recommend two doses of HepB-CpG. I think that two doses has excellent response and is sufficient for the majority of individuals. I do think three doses can be considered on a case-by-case basis. A third dose could be offered if there's suboptimal response to two doses. Though, in my clinic I have found that to be a pretty rare occurrence, or there might be clinical indications to give three doses instead of two. But again, I think that is an uncommon circumstance.

So, the key take-home point of this part of the BEe-HIVe study is that two doses of HepB-CpG given one month apart achieves very high seroprotection rates for people with HIV who have no prior history of hep B vaccination or hep B infection. There may be benefit or indications to give three doses, but I think we need more long-term clinical outcomes data to help answer that question.

paper-2**[11:53] Paper #2**

Marks KM, Kang M, Umbleja T, et al. HepB-CpG vs HepB-Alum vaccine in people with HIV and prior vaccine nonresponse: The BEe-HIVe randomized clinical trial. JAMA. 2025 Jan 28;333(4):295-306. **[PubMed Abstract]**

Next, let's talk about individuals with HIV who have evidence of past hep B vaccination nonresponse. So, this is a different group than I have reviewed so far, and also a very important group because this is something we used to see a lot, especially with older versions of the hep B vaccine. So, this data I will review comes from a second publication of the BEe-HIVe trial. These results were published in early 2025 in the journal *JAMA*, also led by Dr. Kristen Marks.

Now, this portion of the study was conducted differently than the vaccine-naïve part that I previously reviewed. So, I'm going to go through a couple of similarities and differences. Similar to the prior part of the study, investigators enrolled adults with HIV who were taking ART and overall had excellent virologic control. A difference is, for this portion of the study, all enrollees had known past history of hep B vaccination, but no evidence of past hep B seroprotective response to vaccination, meaning no history of achieving a surface antibody level above 10.

overview**[13:18] Overview**

The design of this study was also quite different, so let me go into that a bit. For this portion of the BEe-HIVe trial, it was open label, and there was randomization involved. So, participants were randomized into one of three groups. Group one received two doses of HepB-CpG four weeks apart, group two received three doses of HepB-CpG over the course of six months, and group three received three doses of standard dose traditional HepB-alum vaccine also over the course of six months. So, in this part of the BEe-HIVe trial, what we have is a comparison between an older alum hep B vaccine, a two-dose strategy with HepB-CpG, and a three-dose strategy with HepB-CpG. So, this is really, really clinically relevant.

So, participants in this part of the trial enrolled from 10 different countries; 563 individuals were randomized, so that meant just under 190 participants in each arm of the trial. Now, I won't go into all the characteristics and demographics of participants, but I want to note that there was a wide range of time since the last HepB-alum vaccine dose, and some participants had received quite a few doses of alum vaccine in the past. I think the max was 12 prior doses.

The primary endpoint of the trial was seroprotection at eight weeks after dose number two for the two-dose arm and at four weeks after dose number three for the three-dose arms. A seroprotective response was defined as a surface antibody that rose to above a level of 10.

results**[15:25] Results**

So, what were the key results? Let me just emphasize the key really important findings. Number one, the

seroprotective rates were best for the HepB-CpG arms. They were highest for the three-dose CpG group. The seroprotective response in that arm was over 99%, which is really remarkable. The second-best response rate came from two doses of HepB-CpG. In that arm of the trial, seroprotection occurred for 93% of individuals. And then the lowest response rate was for the three-dose HepB-alum vaccine group. That response rate was 81%. So clearly, the HepB-CpG group did much better than the alum vaccine group, and the response rate was modestly higher for three doses of HepB-CpG compared to two doses. I will go into that in a little more detail.

I also want to point out that the proportion of participants who achieved a surface antibody level of above 100 or above 1,000 were significantly higher with three doses of HepB-CpG compared to two doses of CpG and especially compared to three doses of HepB-alum vaccine. The time to achieve a seroprotective response was also higher in the CpG groups. So, stating that another way, time to protection was shortest with HepB-CpG, and the rates of individuals who achieved very high surface antibody levels was also higher, which may have benefits in terms of durability of protection. And we did discuss durability some in the prior episode reviewing CROI 2025 data, so I would refer you to that as well.

summary**[17:32] Summary**

But let me just come back to the most important takeaway messages here. So, I think the most important and most clinically relevant is that for people with HIV who did not respond to prior hep B vaccination, the seroprotection rates were significantly higher with HepB-CpG as compared to a HepB-alum vaccine. In addition, as I mentioned, seroprotective response was achieved more rapidly with the CpG vaccine strategy, and participants who received CpG vaccine achieved much higher surface antibody titers.

One thing that was slightly different in the findings in this part of the study: Participants who were older or who had lower CD4 counts were less likely to achieve a seroprotective response. So, similar to the prior part of the study, this suggests there might be some indications to give three doses of CpG instead of two. But honestly, in my practice, I have still been doing two doses for the vast majority of individuals. And then approximately one month after the second dose, I recheck the surface antibody level, and I do find that the majority of individuals have achieved seroprotection. But again, that's using a seroprotective level of surface antibody above 10. And I think we still need more data, especially long-term clinical outcomes data, to know better whether achieving a level of above 100 or higher offers more long-term clinical benefit.

I will highlight that in some parts of the world, some guidelines, there is now a recommendation to aim for a surface antibody level above 100 for all individuals with HIV after hep B vaccination. And in some places, there is a recommendation to repeat vaccination when the surface antibody wanes. But so far, that is not the recommendation in this country, and we will see if recommendations or guidelines in this country are updated to reflect some of those changes that have happened recently elsewhere.

So, another point I want to highlight is that the adult opportunistic infection guidelines in this country have been updated and do recommend two doses of HepB-CpG vaccine as the preferred or recommended vaccine. They say that clinicians can consider on a case-by-case basis, giving three doses instead of two, and I agree three doses should be up to clinical judgment and part of shared decision-making, and there may be some situations in which three doses really is indicated. But again, for the vast majority of people in my clinic, I recommend two doses and find that to be effective based on our current thresholds for defining effective.

both-papers-summary**[20:40] Both Papers: A Summary**

So, let me just combine data from the two different publications of BEe-HIVe and just emphasize a couple of points. One, I think there clearly are advantages of HepB-CpG including higher likelihood of seroprotective response, more rapid time to protection, and likely longer duration of protection. So, if you have access to HepB-CpG, if your clinic carries it, I would always prefer that over the alum vaccines. Again, three doses versus two doses of CpG is controversial, and I hope to see more data on that in the future. There isn't a lot of downside to giving a third dose except for cost involved with the vaccine, but as far as we know, a third dose

probably isn't necessary for most individuals. Obviously, the advantage of two doses in addition to cost is fewer injections and completing the series within four weeks. But it may be that in the future we find that achieving much higher surface antibody levels does lead to better long-term durability of protection and over time fewer hep B infections, and that could change our strategy. So, stay tuned for more on that in the future.

Finally, I will just close by giving my clinical opinion and what I think you really should take home from all this review of BEe-HIVe. Again, I really do think data for the benefits of HepB-CpG are convincing. My clinic has switched 100% over to this vaccine option.

Now, if you do not have HepB-CpG in your clinic or don't have access to it, another strategy that has been shown to have benefit over giving standard dose alum vaccine is to give a double dose of that alum vaccine each time you give the dosage. So, each of the three dosages, you could give double the standard dose. Now, that strategy wasn't included for comparison in the BEe-HIVe trial, and it is something I did in the past before the CpG vaccine became available. But again, I really think CpG vaccine should be the priority. If you don't have it in your clinic, advocating to get it I think would be worthwhile.

upcoming-episodes**[23:07] Upcoming Episodes**

Thank you very much for listening to this National HIV Curriculum Podcast series. Please stay tuned for additional episodes about vaccinations for people with HIV. Before closing, I want to note that we will have a future episode dedicated to considerations for individuals with HIV who have isolated hepatitis B core antibody and considerations around vaccination in that clinical situation, which does come up often and can be quite confusing. So, stay tuned for that episode as well. Thank you very much.

credits**[23:42] Credits**

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publications