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Conference Summaries

National HIV Curriculum Podcast

CROI 2025: CARES and BEeHIVe Studies and Their Potential Practice-Changing Impacts

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Season 2, Episode 3

What were the CROI 2025 major scientific research themes and the key findings from the CARES trial on long-acting injectable ART and the BEeHIVe study on hepatitis B vaccines for people with HIV? Dr. Jehan Budak and Dr. Raaka Kumbhakar, co-assistant directors of a Ryan White-funded HIV Clinic, discuss major themes, the two studies, and how their clinical practice has already changed.

Topics:

- OIs and HIV
- injectable ART
- A1 subtype virus
- hepB

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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.

Dr. Jehan Budak is assistant professor of medicine at the University of Washington in the Division of Allergy and Infectious Diseases. She is a provider at the Madison Clinic, which is our Ryan White-funded HIV clinic, and she serves as director of the HIV Pathway through the Internal Medicine Residency. She also serves as associate editor for the National HIV Curriculum. She is an expert in HIV treatment, HIV prevention, as well as general infectious diseases and many other topics.

I'm also joined today by Dr. Raaka Kumbhakar, who is assistant professor of medicine also here at the University of Washington in the Division of Allergy and Infectious Diseases. She delivers care at Madison Clinic and at multiple low-barrier clinics for people with HIV or at risk for HIV. And she dedicates clinical and research time to improving outcomes across the HIV care continuum and to improving systems of care. Like Jehan, Raaka is knowledgeable in many areas of general infectious disease as well and is also a committed medical educator. And, do I understand correctly, Jehan and Raaka, you are also now co-assistant directors of the Madison Clinic?

Dr. Budak

That is correct. And we are sitting right next to each other in our teeny-tiny office.

Dr. Kumbhakar

It's the glamour of co-assistant medical directors.

Dr. Wood

Our listeners won't be able to see that you are sharing an office, which I imagine is nice for consulting on cases, commiserating at times when things get challenging.

Dr. Budak

It's been super fun.

Dr. Kumbhakar

You'll be able to see our shared project agenda behind us on our shared whiteboard, too.

Dr. Wood

And your shared whiteboard with the long to-do list, which I very much understand. Well, I'm really honored to be joined by you both today, and it's great that you're able to join from the same location. And this is going to be fun and I'm really interested to hear your reflections on the scientific themes from what is arguably the most influential HIV-related conference [the Conference on Retroviruses and Opportunistic Infections or CROI] each year. So, without further ado, we'll dive in and talk about it.

major-themes-croi**[02:20] Major Themes at CROI**

I'd like to start with just overall takeaways and themes from the scientific research you heard at the conference this year. Jehan, maybe I can start by asking you. I know you focused a lot on HIV treatment and ART [antiretroviral therapy] studies and also paid attention to other things as well, but what did you take away as the major themes and trends from this year's conference?

Dr. Budak

I always look forward to the treatment topics, as I think you all know. And I'm always looking for updates in injectable antiretroviral therapy for me because that's what we're running here at our clinic. And I think for me, it's really always very helpful to see what are people doing that's new and, I guess, corroborating what we're doing, seeing if others are doing what we're doing as well. And so, I think there was an oral abstract that I'll be talking about, and then many posters actually that I found pretty helpful with regards to how to use cab [cabotegravir]/rilpivirine.

Dr. Wood

That's great. I believe we'll get into some of those in a bit more detail, but that's great just to think about overall trends and future directions. Raaka, maybe I can pose the same question to you. I know you focused a lot on HIV-related comorbidities, but also other topics at the conference. What did you take away as the biggest trends in research and future directions?

Dr. Kumbhakar

Yeah. I think I was focusing a little bit more on comorbidities, as you said, and coinfections. And I think for me that's really interesting, because I think there's a lot of practical implications in our setting. I think when we think about coinfections, we're often looking at really great research coming out of Sub-Saharan Africa or Asia especially with regards to hepatitis B and TB. But I really try to think about how can I change my practice here in the U.S. and Seattle a little bit different. And so, I think there was some nice research in TB and hepatitis B, which I'll talk about today and that I thought was really interesting.

Dr. Wood

That's great. Thanks for sharing that. And it really frames this nicely as what we want to focus on are the

biggest areas of scientific research that may really change our day-to-day practice in-clinic offering care to people who have HIV or people at risk for HIV. So that frames this nicely.

cares-data-96-weeks**[04:34] CARES Data at 96-Weeks**

Kityo, C. *Long-Acting Preexposure Prophylaxis for HIV Prevention*. Randomized trial of long-acting cabotegravir and rilpivirine in Africa \(CARES\): Week 96 results. Symposia. Oral-13 Abstract Session presented at: CROI 2025; March 9-12, 2025; San Francisco, CA. Abstract #202. [**CROI**]

Dr. Wood

And Jehan, leads me to the question: What did you take away as the biggest potentially practice-changing abstract that you saw at CROI this year?

Dr. Budak

So, for me, I guess the one that I'll talk about is the CARES 96-week data that was presented by Dr. Kityo, which was abstract #202. And so, just to make sure that we're all on the same page, the CARES data, we actually first heard about the data from last year at CROI in 2024 in Denver, where they shared the CARES 48-week data. And so perhaps a little bit repetitive since people may be very familiar with the 2024 CROI results and findings. But the CARES is a big randomized trial that came out of Sub-Saharan Africa that was an active-controlled non-inferiority study of about 500 people randomized one-to-one, either oral standard of care or cab/rilpivirine administered every eight weeks with or without an oral lead-in.

And I think, takeaway first, is that it was noninferior. Great. But I think the reason why at least last year things were so exciting was that one, this was a large cohort of individuals from multiple sites in Sub-Saharan Africa, in Kenya, Tanzania, and Uganda. It included 60% women. And, at least in Seattle, that's not necessarily the epidemiology of the epidemic here. And so, I think it's always helpful to see how the medication is being used with different populations. Fifty percent of people in the CARES study had subtype A1 HIV virus, and this is a group of individuals who are very NNRTI [non-nucleoside reverse transcriptase inhibitor] experienced, which is worthwhile knowing, especially when we're giving people cab/rilpivirine.

I think the other thing that was key about the CARES study is that they used a public health approach. And so, basically, just the way I understand it, is recruiting people into the study, getting people into the study, and there weren't necessarily genotypes obtained at baseline, and they were checking viral loads every 24 weeks \(so every six months\), which again is different than what we do here, at least at the Madison Clinic. And so, that was a 48-week data, that was a big recap of CROI 2024. I'm sure you're like, “Jehan, focus on CROI 2025.” And, this year we had 96-week data that showed indeed that it is still noninferior. And Brian, would it be helpful for me to talk a little bit more about the 96-week results?

Dr. Wood

I think people will be interested to hear. What I've heard you say so far is there are some unique aspects in terms of who participated in this trial compared to who participated in the registrational trials that included individuals from North America. So, a couple unique aspects of who participated and a couple unique aspects about how they monitored viral load and some things that make it just very different than the registrational trials here. So, maybe we'll come back to why you think that's important. But if you could go on to summarize the key results, I think that'd be great for listeners.

Dr. Budak

One key thing is, again, as I mentioned, the results between the oral standard of care and the injectable arm were noninferior. And the viral suppression rates were in the high 90 percentiles for both of them. And that was the same at 48 weeks and the same at 96 weeks. Whereas in the 48-week results, there were two

virologic failures in the cab/rilpivirine arm, at 96 weeks, there were four virologic failures in the cab/rilpivirine arm. So, for a total virologic failure rate of 1.6%, which I think is what we've been seeing. And then I think the other thing that was notable is that 81% of people in the study received their shots within the seven-day window. So that's a very treatment-adherent group of individuals on a huge population level doing things in a public health approach. And so, I think that's nice to see. And then also too, as we might expect based on our clinical experience, based on the registrational trials, a large majority of people had injection-site reactions as well.

takeaways-cares**[08:40] Takeaways from CARES**

Dr. Wood

So, what would you say are the biggest takeaways or lessons from this abstract? And how do you think this might affect your clinical practice here in the United States?

Dr. Budak

One thing that, and again, sorry that this already happened in 2024, but was that from the 48-week data when 50% of people had an A1 subtype virus, I think that was a big practice change for a lot of us. Whereas in the prior registrational trials for cab/rilpivirine, such as in ATLAS and FLAIR, we saw a lot of virologic failure amongst the A6/A1 subtype. I think we kind of lumped those two together. And then now, after CARES, I would say I think most of us, at least I do, feel comfortable using cab/rilpivirine in someone with an A1 subtype virus, and it's really just the A6 subtype virus that I'm a little bit still maybe worried or concerned about. And then I think the other thing too, and Raaka can give me a hard time about this, but is the fact that wow, people do well and people do fine not getting a viral load check every single day. I'm being hyperbolic, but you know, like every month. They're, in fact, getting viral loads every six months and doing okay. And so, I think that that is helpful, and I think will really make me feel more comfortable with potentially opening up the frequency with which I am checking viral loads here in our clinical patient population, at least for people who are virologically suppressed, because again, this was a cohort of individuals who were virologically suppressed.

Dr. Wood

Jehan, thanks so much. What I take from this and also adjunctive data about prescribing cabotegravir/rilpivirine for individuals who maybe have a tendency to miss oral ART or have detectable viral loads is there is a lot of potential to expand use of this injectable therapy, potential benefits for people who are not currently receiving it if we can surmount the obstacles to coverage and cost and procurement and all of the logistics. Maybe I'll give you the final word on this abstract before I turn to Raaka and ask her a similar question. But what would you say about the current state of affairs in terms of simply trying to get injectable cabotegravir/rilpivirine for people who may benefit?

Dr. Budak

Yeah, Brian, that's a great question. I think to your point, it has been difficult, and there have been hiccups along the way with the rollout and implementation of injectable ART. And I think that we have seen some places do better than others. But nonetheless, everyone has some difficulty, and there are logistical barriers through the roof, actually, with implementation of this. And so it is, to your point, that's such a nice way to put it, that when something can be done to scale, it can be done well. We can really get this medication to people who need it. And I think it is inspirational to see how this can be done and ways in which we can sort of take it to scale here as well.

Dr. Wood

Absolutely. Jehan, thank you so much.

beehive-data-72-weeks**[11:45] BEeHIVe Data at 72-Weeks**

Marks, K. *The Coinfections: Viral Hepatitis and Tuberculosis*. Highly durable seroprotection with HepB-CpG vaccine in people with HIV \(PWH\): ACTG A5379 \(BEeHIVe\). Oral-02 Abstract Session presented at: CROI 2025; March 9-12, 2025; San Francisco, CA. Abstract #112. [**CROI**]

Dr. Wood

I'll switch gears. Raaka, would love to ask you the same question. As you sat at CROI and heard a lot of really fascinating research abstracts, what did you take as potentially the most practice-changing study you saw?

Dr. Kumbhakar

Yeah, I think I'll stick to a similar theme as Jehan in that it's really the longitudinal data from a study we've already heard a lot about, and that's the BEeHIVe study. So, just to remind everyone that's, I'm reading it because it's hard to remember “B-Enhancement of Hep B Vaccination in Persons Living With HIV.” And so that was Kristen Marks' team. And this data has been presented many, many times, starting in 2022 at IDWeek, I believe was the first time we saw data. And I'll go into the nitty-gritty in a second, but this is the 72-week durability data for the use of HepB-CpG. And I'll just say it once: the brand name is *Heplisav-B*. I'll say HepB-CpG or try to from here on out.

Dr. Wood

Sounds great. And I will try to do the same. It's challenging at times. So, this is longitudinal, longer-term follow-up data. And Raaka, maybe if you could remind listeners the design of the study and who participated and then go a bit into what you see as the really key potentially practice-changing results here.

Dr. Kumbhakar

Sure. Thanks, Brian. So, basically, the whole premise is that we know that hepatitis B seroprotection in people with HIV is lower than people without HIV when they get conventional hepatitis B vaccination, which is with an alum adjuvant hep B vaccine. And so, what this study looked at and was really interesting was two arms. One was people with HIV who are hepatitis B prior vaccine non-responders, and then arm B was the hep B vaccine-naïve group. And then, within the non-responders, there's three arms. People got either two doses of HepB-CpG, three doses of HepB-CpG, or three doses of the conventional alum adjuvant. And then, in the vaccine-naïve arm, everybody got three doses of HepB-CpG.

People who were in the study were all people with HIV; they were on ART, they had to be virally suppressed. They had relatively high CD4 counts. So, the inclusion criteria was a CD4 greater than a hundred. When we go in the data, the median was much higher, in the 600s. It was a pretty high nadir actually, in the 200s. People had to not have hepatitis B, obviously. They couldn't be pregnant. And people who were non-responders had to have a defined low surface antibody titer of less than 10. And as a reminder, 10 is our threshold for, in people who don't have a positive core antibody; that's the protective threshold. And that's basically who was in the study.

And so, just to recap, I think that was the second part of your question, Brian, of what has been all the stuff that's been presented before. And so, in the non-responder arm, really the takeaway is everyone did better with HepB-CpG. So, in arm A in the non-response group, people who prior didn't have a good response, superior responses with CpG as compared to alum. And if they got more doses, they had a higher surface antibody response. And I want to be careful and say higher and not necessarily say better because I think that's going to be something we talk about. But people who got three doses of HepB-CpG were more likely to get a surface antibody of greater than a thousand. So, remember that 10 was our cutoff, and we're up to a thousand here. In the vaccine-naïve arm, arm B, all people with HIV who got the three-dose HepB-CpG series got a seroprotective response, and 84% had that threshold of greater than a thousand. Ninety-nine percent

had a seroprotective response after just two doses, though at slightly lower titers. But even then, a third got to above a thousand. So that was everything that's happened so far.

I'll pivot now to what happened in this study. So again, this is the 72-week results. Basically, everyone still had a very durable response, but in Group A, I'll say that at the end of study, who still had a surface antibody greater than 10, that was 97% in the three-dose CpG arm, 86% in the two-dose CpG arm, and a pretty dismal 57.5% in the three-dose alum arm. So, the other thing to note that among the people who achieved SPR \(so the seroprotective response\) at any time in the study but then lost it by study end, that was only 2.1% in the three-dose arm, 10.7% in the two-dose CpG arm, and 22% in the three-alum arm. Then, if I switch to Group B, the end-of-study anti-[hepatitis B] surface antibody greater than 10 was 97% in the three-dose arm, which was comparable to the three-dose group in Group A, and the durability now is a 100% for primary seroprotective response, and then end-of-study seroprotective response was 97%. So, I'll pause there because there's still some more data on durability, but I know that's a lot. And Brian, I'm curious if you have anything to add or ask in between.

Dr. Wood

No, that's fantastic. I do want to interject a question here. Raaka, it seems overall to be very convincing data that HepB-CpG leads to much higher responses than the alum vaccines we used to use.

hepb-cpg-use-clinics**[17:25] HepB-CpG Use in Clinics**

Dr. Wood

So, I just want to ask in terms of translating this to clinical practice, to what degree have you switched in your practice to using the HepB-CpG?

Dr. Kumbhakar

So, here at Madison, everyone is now getting HepB-CpG. Even from the prior data, pretty convincing that this is just going to get a better response.

Dr. Wood

So, really, a 100% you have crossed over to using HepB-CpG for individuals with HIV either who have never had hep B vaccine and have an indication or for those who have not had a seroprotective response to the older versions of the vaccine. Is that correct?

Dr. Kumbhakar

That's correct.

Dr. Wood

Okay. So maybe there, do you want to go into a bit more about the durability of response?

Dr. Kumbhakar

So, what I've just talked about is that it's still durable at 72 weeks. Very few people who achieved their response lost their response. But I do want to highlight that the biggest takeaway to me was that the higher primary titers of surface antibody response were more likely to lead to end-of-study seroprotection. And so, that was kind of the question to, I think, many of us, is, does it matter if you get to above a thousand? And what we saw that a 100% of those who had titers of greater than a thousand at their primary response still had that end-of-study response. Now, that attrition rate may not be that dramatic as we saw, but I think it

really is meaningful in thinking about what is our durability over time.

And why does that matter? I think you've heard Jehan talk about now cab/rilpivirine. We're talking about a lot of switches to two-drug therapies that don't have tenofovir in them. We know that tenofovir acts as a kind of hepatitis B PrEP [preexposure prophylaxis]. And so, I think when we think about what's going to happen, do we just vaccinate and say, “You're good to go for the rest of your life, we never have to check again, we never have to do anything.”? I think the jury's still out in terms of real RCT [randomized controlled trial] data about what it means clinically, but I think I'm pretty convinced it's better to get higher faster and then not worry about it.

Dr. Wood

Absolutely. So again, just coming back to clinical practice, sounds like you've really moved to only using this new version of hepatitis B vaccine. The other question I get asked a lot is two doses versus three doses because there were three-dose arms in the study. What are you doing in practice? Is there anyone for whom you are really encouraging three doses right now?

Dr. Kumbhakar

Yeah, great question. And I think this study or this data rather has kind of refined my stance, I would say. So, I think that for most people I've said two is enough. We have sufficient data to say that you're really getting high titers by two doses, especially if you have a high CD4 count. So, there’s a caveat that because we don't see people with pretty low CD4 counts in this study, that might be a population I might push to try to get three doses in to see if we can really get to a higher antibody response since we know that might be less likely upfront. I do think that there is a role for checking that surface antibody, which we do, and then making a decision, a shared decision with the patient, and saying, “You know, you didn't really get quite up there. Let's try one more.” But I think it's really compelling to be able to say, “Hey, you can get two doses a month apart, and then you're set.” And so, for many, many people, I'm just saying that check a surface antibody a couple months later whenever they're next in and saying, I think we're okay. And maybe if they're switching to a two-drug therapy off tenofovir, I'll check again. And this is kind of, I'm making it up a little bit, but it might make me feel a little bit better.

Dr. Wood

Yeah. That point is very well taken. And it's a great reminder to think about hepatitis B status and serologies before considering a switch of ART, especially a switch of ART to a two-drug option and especially an option that avoids any version of tenofovir to an option that avoids TAF [tenofovir alafenamide] or TDF [tenofovir DF] for example. So then, Raaka, maybe last question, and I think this one is challenging because I haven't seen good guidance, but what if someone in the past had a level of surface antibody that was protective and for whatever reason, it's rechecked and it has waned down to below 10, below the titer considered protective. May I just ask what you are doing in your practice in that circumstance?

Dr. Kumbhakar

Yeah, I know we talk about the anamnestic response in hepatitis B, and yet we've had a handful of anecdotal cases, and I know we've had some here at Madison. Last time I was at the Ryan White Clinical Conference, I spoke to some people who had seen some reports of people who had lost that response and then acquired hepatitis B, again, off of tenofovir-based therapies. And so that to me is enough to say let's just revaccinate; it can't hurt. And now, at least, I can say with *Heplisav-B* \(or HepB-CpG\), one dose is probably enough to really rocket you up there.

Dr. Wood

So, really a lot of convincing data for the benefits of HepB-CpG for practitioners who maybe haven't made

that switch in their clinic yet. It sounds like what you are both doing in your clinical practice. Jehan, I've seen you nodding, which our listeners won't be able to see, and it really does sound like the data's convincing for the benefit over the older alum vaccines.

Dr. Wood

So, this is fantastic. We heard a lot about HepB-CpG, heard a lot about new data for injectable cabotegravir/rilpivirine. So, I want to thank you. We'll end this episode there. And I'm looking forward to another conversation about the important data from CROI. Thank you both.

Dr. Kumbhakar

Thanks so much, Brian.

Dr. Budak

Thank you.

credits**[22:42] Credits**

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potential-practice-changing-impacts