Conference Summaries

National HIV Curriculum Podcast

CROI 2025: Four More Potentially Practice-Changing Abstracts

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Season 2, Episode 4

Dr. Jehan Budak and Dr. Raaka Kumbhakar, University of Washington Assistant Professors of Medicine, discuss CROI 2025 abstracts on the complexities of treating TB during pregnancy, the use of tenofovir alafenamide for people with TB, switching to the investigational ART combination doravirine/islatravir, and data on why people stop injectable cabotegravir/rilpivirine.

Topics:

- OIs and HIV
- TB
- islatravir
- CAB/RPV

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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.

Well, today I'm very honored to be joined by two colleagues. Dr. Jehan Budak is assistant professor of medicine here at University of Washington in the Division of Allergy and Infectious Diseases. She provides care at the Madison Clinic, our Ryan White-funded HIV clinic, and is also director of the HIV Pathway through the Internal Medicine Residency. She serves as associate editor for the National HIV Curriculum and is an expert in many topics related to HIV and general infectious diseases.

We are also joined by Dr. Raaka Kumbhakar, who is assistant professor of medicine here at University of Washington as well. She's also in the Division of Allergy and Infectious Diseases, and she's a provider at the Madison Clinic as well, plus multiple low-barrier clinics for people with HIV. She does a lot of really important work to help improve outcomes along the HIV care continuum. Like Jehan, she's knowledgeable in many topics related to HIV treatment and prevention and general infectious diseases. And we learned during the last episode, Jehan and Raaka are also now co-assistant directors of our Madison Clinic here.

I am honored to be joined again by both of you, Raaka and Jehan, and looking forward to this conversation.

Dr. Budak

Thanks Brian.

Dr. Kumbhakar

Thank you.

Dr. Wood

So, let's just dive right in. So, really this time I'd like to start with another major potentially practice-changing abstract that you saw at CROI. Something that really hit home for you in terms of the scientific research and findings, and something that really could change practice in the future.

So, Raaka, if you would start, what would be your choice number two, because you gave me choice number one last time, what's choice number two for potentially practice-changing abstract from CROI this year?

tb--pregnancy-overview**[02:03] TB & Pregnancy Overview**

Mathad J. *The Coinfections: Hepatitis and Tuberculosis*. DOLPHIN-Moms: pharmacokinetics of dolutegravir and HIV viral suppression with 1HP or 3HP in pregnancy. Oral-02 Abstract Session presented at: CROI 2025; March 9-12, 2025; San Francisco, CA. Abstract #116. [**CROI**]

Dr. Kumbhakar

So, I will pivot from hepatitis B last time to TB and pregnancy. And so, there was an abstract called, and again, I don't take credit for naming any of these, DOLPHIN-Moms, which was great, and that was Mathad et al. And what I really liked about this is it talks about two populations that I don't think of so much in my immediate practice until it happens, which is women who are pregnant and who have TB at the same time. And so, DOLPHIN-Moms looked at the pharmacokinetics (PK) of dolutegravir and HIV viral suppression with either of the short course rifapentine latent TB treatment options. So, 1HP or 3HP.

And what I liked about this is that I think it was really practical and these are investigators who really thought about a population that is often overlooked or forgotten and were really systematic about their approach. And they highlighted some things for me just in the background that I don't think about that often and were really jarring. So, for women with HIV, active TB risk is highest during and just after pregnancy. We have these short course options, which I'll go into a little bit more, but pregnant women were excluded from the trials of 1HP and 3HP. And that's because dolutegravir troughs, we know, drop in pregnancy. And so, then they weren't even included. And so, then you have daily isoniazid that we're left with for pregnant women with TB.

But, there's RCT [randomized controlled trial] data that there are increased pregnancy adverse events in 6H (or six months of isoniazid). And so, that's led some countries, like South Africa, to say just defer treatment for now. But we know active TB risk is highest in pregnancy and, obviously, having active tuberculosis in pregnancy is not going to be good for mother or child. And so, that's why I really thought this was a nice abstract to highlight.

design--results**[03:52] Design & Results**

Dr. Wood

Yeah, that's a great abstract, Raaka. Maybe you can dive in a little more detail in terms of the design of the study and the key results and takeaway messages for listeners.

Dr. Kumbhakar

Sure. What happened in this trial, this is a phase two RCT of 1HP. Sorry, I should go back and define these explicitly. So, 1HP is one month of daily isoniazid and rifapentine; 3HP is weekly isoniazid for three months with rifapentine; 3HP comes with daily dolutegravir and 1HP has twice-a-day dolutegravir. And, this is for women who are not pregnant living with HIV.

In DOLPHIN-Moms, they looked at 1HP and 3HP in pregnant women and the pharmacokinetics of dolutegravir. So, they had two arms. So, there was daily 1HP with twice-a-day dolutegravir. And then arm two was the weekly 3HP with also twice-a-day dolutegravir. And the rationale here is the point I briefly mentioned about

the dolutegravir troughs being lower in pregnancy. And so, they said we just have to give everyone twice-a-day dolutegravir upfront to test this theory because it wouldn't be ethical or safe otherwise.

And so, everyone had been on a dolutegravir-based therapy for a month or more with viral suppression. And again, these are pregnant women with latent TB and because this is a high-incidence setting, this is framed as tuberculous preventative therapy, but analogous here to what we think about as LTBI [latent tuberculosis infection]. And then they looked at PK parameters of dolutegravir in both of these arms. So, these were pregnant women who were in their second or third trimester, their week one and day zero was a randomization at 20 to 34 weeks of pregnancy. Then on day one, they were initiated on their therapy, and they got a day-one dolutegravir level prior to their starting the rifamycin (the rifapentine). And then they got a day-one level, then they got a day-17 level in both arms, and then they got a day-52 level in the 3HP arm.

If you look at this abstract, the plots are confusing because they got an 11- and 12-hour level, and I think to be really specific about when do these peak, and so that they could input these values into their model, which I'll admit the math was far beyond me. But, made sense. And so, that's what they did to set this up and they looked at the first 25 participants in each arm because this is a larger, as you can imagine, safety and tolerability trial.

And then what happened? So, I think the big takeaways, day one, as you can imagine, there was no difference in dolutegravir levels between the arms. By day 17, in both arms, there was a significant drop in dolutegravir, but it was above what we consider in most previous data to be a therapeutic dolutegravir level. That level was lower in 1HP as compared to 3HP, perhaps unsurprising. And then by day 52, there's stable levels. There was just a few, was just two, who fell out of that therapeutic range of dolutegravir. But the long story short is they were pregnant women who had adherence difficulties and were able to correct for that once they were taking their medication appropriately again.

So, that was exciting. Well, I'll pause because Brian, you wanted to ask about the PK modeling, right?

pk-modeling**[07:10] PK Modeling**

Dr. Wood

I do want to ask about the PK modeling, but I mean so far, I really appreciate the points that this is a really important study to do. These are things that are not often included in randomized control trials, things like latent tuberculosis and pregnancy is often exclusion criteria for trials. So, just coming back for listeners to the importance of this, thinking about options to treat latent TB during pregnancy, and really this question of what dolutegravir dose is best and can once-a-day dolutegravir be used. So, I agree with you so far, this is very exciting data and maybe now yes, you can get into the PK modeling because I think some important lessons came out of that.

Dr. Kumbhakar

Thanks Brian. So, I think, as we'll remember, in the way they've set up the trial, everyone is getting twice-a-day dolutegravir. Right? But then they used their dolutegravir troughs to say, what if we simulated what it would be like to give daily dolutegravir with both regimens, both the 1HP and the 3HP. And so, for the 1HP in their simulation, unfortunately this wouldn't work. All the dolutegravir troughs would fall below target. But in 3HP, they all remained above target, so they were therapeutic. And so, this is again PK modeling, but it was enough to suggest to them that it would be reasonable to trial and then ongoing in the trial daily dolutegravir with the 3HP arm, not the 1HP.

Dr. Wood

So, just to summarize that, so promising or potential for daily dolutegravir dosing with 3HP, but as far as they could tell from the results in their modeling with 1HP, twice-a-day dolutegravir is probably or is what they

suspect will be necessary. Did I understand that right?

Dr. Kumbhakar

Yeah, that's right. And I think they won't even test the theory in 1HP because it was pretty convincing. And again, remember this is still the recommendation in nonpregnant women, so it's perhaps not surprising. But it's great that they tested the theory, but they'll go on and say, what if we can test daily dolutegravir in 3HP?

Dr. Wood

Got it. So, more data coming in the future.

Dr. Kumbhakar

Exactly.

Dr. Wood

Raaka, I appreciate that a lot and really glad you brought up this topic for us to think about. It is very important. Raaka, for time I'm going to switch gears. But I appreciate that a lot and I'll be flipping back to you here in a bit.

switching-to-dorisl**[09:30] Switching to DOR/ISL**

Dr. Wood

Jehan, I have the same question for you. You gave us number one top pick abstract from CROI last time we talked. What's your pick number two?

Colson A. *Late-Breaking Antiviral Therapy: It Doesn't Get Any Hotter Than This!* Switch to DOR/ISL (100/0.25 mg) QD From BIC/FTC/TAF: A blinded phase III study in adults with HIV-1. Special Session. Oral-13 Abstract Session presented at: CROI 2025; March 9-12, 2025; San Francisco, CA. Abstract #204A. [**CROI**]

Orkin C. *Late-Breaking Antiviral Therapy: It Doesn't Get Any Hotter Than This!* Switch to DOR/ISL (100/0.25 mg) QD from oral ART: An open-label phase III study in adults with HIV-1. Special Session. Oral-13 Abstract Session presented at: CROI 2025; March 9-12, 2025; San Francisco, CA. Abstract #204B. [**CROI**]

Dr. Budak

I think I'll talk a little bit about the doravirine/islatravir (DOR/ISL) studies, which were two paired oral abstracts. The first one was presented by [Amy] Colson, and that was number 204A. And then the second one was presented by Dr. Chloe Orkin, and that was 204B about this combination as a single-tablet option.

And so, I think as background, islatravir is an NRTTI, which stands for a nucleoside reverse transcriptase translocation inhibitor. And a couple years ago it was being studied, but as we might all recall, it had to be halted due to drops in the CD4 count and the total lymphocyte count, which was attributed to the islatravir. And, my understanding of that is that it was a dose-dependent issue, it was reversible. And then they decided to sort of redo these studies after what seemed like a long time, even though I know it wasn't a long time, but we've been waiting to see what's going to happen with islatravir. And so, they redid these studies with 0.25 milligrams, whereas in the previous studies where we had seen those issues was 0.75 milligrams. And I was curious as to why that was happening. And what I was able to find out was that islatravir, I think, triphosphate accumulates in the lymphocytes and then actually causes an apoptosis, which is why the cells were

decreasing. Anyhoo.

So, what they did here was, again, just repeat the studies with 0.25 milligrams of islatravir paired with doravirine. And so, these, as I mentioned, two studies, both had about 500 individuals with HIV who were virologically suppressed. The first study was a double-blind study where people were on TAF [tenofovir alafenamide], FTC [emtricitabine] and bictegravir (or BFTAF), and they were randomized 2:1—islatravir/doravirine (ISL/DOR), or to continue on their current regimen.

And then the second study was an open-label study and the people were on baseline ART [antiretroviral therapy]. And from what I recall, about 64% of those individuals were on an integrase-based regimen; similarly randomized 2:1 to being on islatravir/doravirine versus staying on their baseline ART. And, the big takeaway point was that the viral suppression rates were similar and thus was noninferior.

And, I think what was significant about this is I believe, is that initially when things had to be halted after the 0.75 milligram dose was causing issues, I think people wondered how potent will 0.25 milligrams be, and in fact seems that it was potent enough. So, that was kind of a big deal.

Dr. Wood

If I'm hearing correctly. So, this lower dose of islatravir seemed to retain virologic efficacy when paired with doravirine and did not have the deleterious effects on CD4 count or lymphocytes the higher doses did. Is that correct?

Dr. Budak

Correct. Yes.

metabolic-outcomes**[12:34] Metabolic Outcomes**

Dr. Wood

So, this is the potential for a switch therapy to a two-drug combination doravirine/islatravir. So, the question in my mind, let's start with who might be good candidates for this potential switch in the future. Who are you thinking about in your practice? And then as a corollary, one thing I've read about doravirine/islatravir is it is postulated that both drugs are fairly metabolically neutral. They may not stimulate excess weight gain or metabolic complications, which is a concern that's been raised in recent years with some other antiretroviral medications.

So, can you go a little bit more, Jehan, into any metabolic outcomes from the studies? And then who are you imagining in your practice might be good candidates for this two-drug therapy?

Dr. Budak

Okay, so first is the metabolic stuff. So, I think to your question, Brian, my understanding was, at least it was in the study where they were comparing things to the baseline ART not to the BFTAF, they did notice that with removal of the baseline ART, there was some weight gain in the DOR/islatravir arm. That being said, my understanding was that that was because of removal of either TDF [tenofovir DF] or efavirenz. And so, thus removal of the anorectic medication then led to some weight gain. And then, I remember seeing an image where they compared if you weren't on tenofovir or efavirenz and then it was weight neutral. I do think of this as a relatively weight-neutral medication option.

And then to your second question about who are we going to use this in? In fact, I think, Raaka, and our other colleague came out of the oral abstract and we're like, well, who are we going to use this in? And I feel like we were talking about this in the cafeteria as well, where it's like, who is the person going to be for this? I think

as the investigators pointed out, it's the first two-drug regimen that doesn't include an integrase inhibitor. Right? Like, the other two-drug regimens are dolutegravir/3TC [lamivudine], dolutegravir/rilpivirine, and CAB [cabotegravir]/rilpivirine. And so, this is one that doesn't include that. And I know, and to your point, there has been discussion and concern about potential metabolic effects with maybe some of the integrase inhibitors. And so, this would be sparing of that and include that. So, I think it could be a weight-neutral option is one thing.

And I think for me, and this is by no fault of anyone's, it's just that I would like to see a little bit more observational data with regards to islatravir, like how durable is it? I know it's potent enough, but what's its barrier to resistance? How is it in real life? So that I can get a better sense and get more familiarity. But I would like a little bit more observational data before I start using this combination in individuals to really figure out what its point is going to be. And I think because we had to wait a little bit more for the new data at the lower doses, we just don't have that information yet for me to figure out exactly who I'm going to be using this single-tablet regimen or this, rather, combination of meds in. Also too, I think they're going to pair islatravir with other medications as well. And so, we'll see what its role is there, if it's not here.

Dr. Wood

Absolutely. And to add to that, I think it may end up being that we see islatravir paired with other medications that could have lower dosing frequency, potentially even once-per-week dosing, for example. Is that correct?

Dr. Budak

Yes. And in fact, at CROI 2024 there was a poster, I believe, about weekly islatravir with weekly lenacapavir, if I recall correctly, and I think there are some other things out there too.

Dr. Wood

So, potential for new two-drug combinations that do not include integrase inhibitor, maybe a little further down the road potential for two-drug options, a switch therapy that even has less frequent dosing and may not require taking pills every day. So, a lot of promising potential here.

Dr. Budak

Yes.

Dr. Wood

Jehan, this is great. Okay, I'm going to move us to the next segment of this.

taf-tb-therapy**[16:40] TAF and TB Therapy**

Dr. Wood

And really, what I'm asking you for here is less of a deep dive, but more quick hits if you will.

Raaka, I'll turn to you next. What would you take as a quick hit takeaway that listeners should be aware of?

Mpofu R. *Drug-Drug Interactions and Pharmacology Challenges With Important Coconditions*. TAF achieves adequate intracellular tenofovir-DP concentrations with rifampicin-based TB therapy. Poster Session F-02 presented at: CROI 2025; March 9-12, 2025; San Francisco, CA. Poster #646. [**CROI**]

Dr. Kumbhakar

So staying on the TB theme, there was a poster by Mpofu that was Poster 646 that I thought was really interesting, that basically proved our point that it is okay probably to use TAF with rifampicin-based TB therapy. And I think this is important because many people will say, “duh, well, we're already doing that,” or “there's higher intracellular concentrations of tenofovir with TAF than TDF. We already know this.” But the FDA label still says, don't co-administer TAF and rifampin (RIF). The OI [opportunistic infections] guidelines say you can do it, but monitor closely. And what this study looked at was they looked at pKa on people who were virally suppressed on rifampin-based therapies, and they did sampling of intracellular tenofovir when they were on TDF plus RIF, on TAF plus RIF, and then at the end, when they were on TDF alone. And throughout all of that, the intracellular tenofovir concentrations were highest in TAF even though, recall, that was with RIF. It was still even higher than TDF alone. So, I think that's really reassuring to me that that study had been done or a similar study had been done in healthy volunteers without HIV, but to say, hey, look, they're fine, their intracellular levels are fine, they remain virally suppressed. I think that's really compelling, especially as we ask people to change around their regimens while they're getting treated.

Dr. Wood

Absolutely. So, have you done this yet in clinical practice? Have you prescribed TAF with a rifamycin?

Dr. Kumbhakar

I think what has happened is I've opted not to change someone’s TAF-based therapy. I think what we more often run into, as you know, is the integrase issue. So, if someone is on BIC/TAF/FTC, we still run into the issue of the bictegravir (BIC) level. So, I'm still switching people off of that regimen onto TDF backbone. But now, I think there's been a couple of cases where we've paused because someone needs TAF versus TDF because of a renal issue. And so, now I feel a little bit more compelled to say, hey, we can do this. You don't need six months of isoniazid. You have a few more options available to you.

Dr. Wood

Some reassuring data that if someone is taking, let's say TAF/FTC as their NRTI [nucleoside reverse transcriptase inhibitor] backbone, there's a reason not to switch it or it would be challenging to switch it, that prescribing it along with a rifamycin for LTBI or TB treatment really looks like it should be okay. And as you mentioned, the OI guidelines say if you do that, maybe monitor the viral load a little more closely, but really this is reassuring that that combination should be fine. Am I hearing that correctly?

Dr. Kumbhakar

Yeah, that's exactly how I'd frame it.

Dr. Wood

I agree that is a very potentially practice-changing research abstract, so that's great. I'm glad you brought that one up.

why-do-people-stop-cabrpv**[19:40] Why Do People Stop CAB/RPV?**

Dr. Wood

Jehan, I'm going to turn to you. One or two quick hits, faster, more lightning round. What do you think listeners should be aware of?

Christopoulos K. *Long-Acting Therapy: What Observational Data Tell Us About the "Real World"*. Why Do People With HIV Stop Long-Acting Injectable Cabotegravir/Rilpivirine and What Happens? Poster Session G-02 presented at: CROI 2025; March 9-12, 2025; San Francisco, CA. Poster #683. [**CROI**]

Faggiano T. *Long-Acting Therapy: What Observational Data Tell Us About the "Real World"*. Outcomes in Those Who Discontinued Injectable Cabotegravir/Rilpivirine and Resumed Oral ART. Poster Session G-02 presented at: CROI 2025; March 9-12, 2025; San Francisco, CA. Poster #685. [**CROI**]

Dr. Budak

So, this is not necessarily practice-changing per se, but I think it's been helpful to see what's been going on with injectable CAB/rilpivirine. And in fact, since it's been FDA-approved in 2021, we now have enough data that there were actually two abstracts talking about why people stop using CAB/rilpivirine. And so, that one was Kat Christopoulos, and that was, I believe, poster number 683 from Ward 86 data in San Francisco. And then [Tali] Faggiano had a poster from the Owen Clinic at UCSD, and that was poster number 685. Both were retrospective cohort reviews of about 450 people with HIV that had been on CAB/rilpivirine. I think the Ward 86 group had about a year and a half worth of data. And then the Owen Clinic had about half a year worth of data. And interestingly, about maybe 16 to 20% of people had actually stopped CAB/rilpivirine after having initiated it. And the main reason for discontinuation was injection-site reactions, but also logistical issues coming in, planning, scheduling, et cetera, were another one.

And I think that that's, again, this is just helpful because we have some observational data about what's going on as people are using this medication. And, though there is a lot of satisfaction with it, there's a decent number of people who are actually stopping because of the injection-site reactions. And so, it was just helpful to see.

Dr. Wood

The lesson I take from that, and maybe listeners can take is if you are gearing up to prescribe injectable cabotegravir/rilpivirine, counseling individuals about the potential for injection-site reactions, having a plan to help to minimize those to help if they do occur, I mean, really is an important part of the therapy.

Jehan, do you have any anecdotes from your clinic and your practice of any strategies that help to reduce the painful reactions or help if someone is experiencing them?

Dr. Budak

What I've heard is stuff like hot compresses, using over-the-counter NSAIDs, maybe some ice. And then, I've also heard some people doing squats the day of, in which I think physiologically makes sense to me to maybe get blood flow moving and doing many squats over the course of that day to help mitigate that. And so, I think that that's one thing. And I think we've seen some people here stop due to injection-site reactions. I'm not saying that 16 to 20% of people stop because of ISRs (or injection site reactions). It's just that 16 to 20% of these people in these cohorts stopped for a variety of reasons. ISRs happen to be the big one.

And I think what is really important for patients to know is that when you're starting an injectable antiretroviral therapy, it doesn't necessarily have to be a forever thing. It can be a part of your life. It's not a destination. It is just something that they can be on for a short amount of time and may not be forever, and that's okay.

Dr. Wood

Yeah. No, that's well said. And if an individual has trouble tolerated it, they can talk to their clinician about a transition back to oral ART.

Dr. Budak

Totally. Just like any other medication.

Dr. Wood

Absolutely. This was great. Again, I think really helpful to hear potentially practice-changing research abstracts from the conference. I'm sure there are many, many more we could have talked about, but it sounds like these are the ones that stood out to you the most. So, Jehan, Raaka, I want to say another huge thank you for sharing your time with me today.

Dr. Kumbhakar

Thanks so much for having us.

Dr. Budak

Thanks, Brian.

Dr. Wood

Thank you.

credits**[23:26] Credits**

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