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Expert Interviews

National HIV Curriculum Podcast

Cardiovascular Side Effects of Antiretroviral Therapy

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Dr. Chris Longenecker, a University of Washington Associate Professor of Medicine, discusses the cardiovascular side effects, including effects on lipids, of common antiretroviral therapy (ART) drugs with National HIV Curriculum Podcast Lead Editor Dr. Brian Wood.

Topics:

- CVD and HIV
- cardiovascular disease
- ART

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Disclosures

Disclosures for Chris Longenecker, MD
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None

Transcript

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In this episode:

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.

As background, we know that the population of individuals with HIV is aging. We know there are compelling data showing that persons with HIV have higher rates of major adverse cardiovascular events as compared to persons without HIV. It is also clear that certain antiretroviral (ARV) drugs may impact cardiovascular risk in adverse ways and certain agents may be favored over others in the setting of cardiovascular disease (CVD) or other cardiovascular risk factors.

And, today, we are honored to welcome back Dr. Chris Longenecker to discuss this issue. Dr. Longenecker is associate professor of medicine in the Division of Cardiology and the Department of Global Health here at University of Washington. He is the Inaugural Director of the Global Cardiovascular Health Program, as well as Director of our HIV cardiology clinic at the local Ryan White-funded HIV primary care clinic. He's a renowned researcher on mechanisms and prevention of cardiovascular disease for people living with HIV, and we are lucky to have him back. Welcome, Chris.

Dr. Longenecker

Thank you very much, Brian. It's a pleasure to be here as usual.

abacavir**[01:24] Abacavir**

Dr. Wood

Well, I'm excited to be talking to you again and this is a very important topic. It's come up for me a lot in clinic, working in our HIV primary care clinic, and I'm really interested to get your expertise and insights. And, again, we'll focus on cardiovascular side effects of ART [antiretroviral therapy] and how you consider different classes, different drugs, and what comes up for you in clinical practice. So, let's dive in and let's start with NRTIs [nucleoside/nucleotide reverse transcriptase inhibitors], and I'd like to kick things off with abacavir. There was so much controversy for years over whether abacavir truly raised risk for ischemic cardiovascular events, but I feel like data has accumulated. I feel like more and more experts believe that abacavir truly causes cardiovascular issues, but I'd be really interested to get your take.

Dr. Longenecker

Yeah. Well, first, I agree with you, but I want to acknowledge that I think that it's kind of becoming a bit of a non-issue, or certainly less and less of an issue, in both high- and low-income countries alike, given that most modern ART regimens do not include abacavir, in my experience, and I'm not a treating HIV doc. But the people that are coming through my clinic at least, I feel like clinicians are getting a lot more comfortable with prescribing TAF [tenofovir alafenamide] for patients with CKD [chronic kidney disease] and so that traditional dichotomy of putting people with CKD on abacavir, we don't see that as often. So, fewer and fewer patients on abacavir.

Nonetheless, I do believe that there is likely to be a cardiovascular risk with abacavir, given the totality of all the evidence. And, you know, I would start with the initial study from the D:A:D study, the epidemiologic study that suggested that current abacavir use was associated with cardiovascular events but not cumulative. So, there was something about taking it that affected your risk. And then that subsequently was followed up

with a subsequent paper from the D:A:D study, showing that the signal for risk persisted even after 2008 when they initially published their findings.

Then there were a series of papers on trying to figure out the mechanism and pointing towards platelet reactivity, potentially, maybe something about inflammation, but really platelet reactivity being the key mechanism at play, which would make sense then if current use was associated risk, because it's pro-thrombotic. But there's not necessarily a cumulative risk. And then interestingly, there was another follow-up study from the D:A:D that showed people who have a myocardial infarction or stroke or some ASCVD event but continued abacavir anyway compared to those who were switched off of abacavir, there was no signal for risk. So, why might that be? They speculate—obviously, this is not a randomized controlled trial—but they speculate that may have to do with the antiplatelet drugs that are prescribed to people for secondary prevention. So, it's kind of a nice through line. It's a story that explains everything and in the end makes sense to me, so I kind of believe that story. I think there are still people who don't, for whatever reason who think that it's some sort of channeling bias or something in the epi data. But from my perspective, it seems like a real effect.

Dr. Wood

That is a nice through line and sounds very biologically plausible, and I appreciate the way you summarized that history of the issue and it's helpful to know that you believe the effect is real or can be real.

hla-b5701**[05:00] HLA-B*5701**

Dr. Wood

I will maybe go back to the start of your comment and just confirm. In my own clinical practice, I've gotten away from prescribing abacavir not only for this issue but also the required HLA-B*5701 testing.

Dr. Longenecker

That’s true, yeah.

Dr. Wood

I just find that a lot of individuals, even who are B*5701-negative, don't tolerate it as well, and the combination tablet with dolutegravir, lamivudine, and abacavir is a really large tablet and then you add this issue, and I think there are a lot of reasons why we are opting for other options in clinical practice. So, when you do come across someone in your clinic taking abacavir still, let's say they're tolerating it well, their viral load is suppressed, but they have other cardiovascular risk factors, how do you counsel them or how strongly do you encourage them to switch for another option? How does that go for you in your practice?

Dr. Longenecker

Yeah, I think if someone is still on abacavir, despite all of those reasons you mentioned, there must be a good reason, whether it's a personal one, they're just really attached to it or something that I'm typically not going to recommend switching off of it. I think it is just one more factor to consider in their atherothrombotic risk and weighing that potential benefit of aspirin for primary prevention. So, I have typically, in the years that I've been doing this over the last 10 years running an HIV cardiology clinic, I can think of two or three times where I might have just brought it up and they're like, 'Oh yeah, I'm not sure why he’s still on abacavir. Let's switch the drug.' So, it's a very rare occurrence.

Dr. Wood

That's helpful to hear and a good reminder to consider it, and there are a lot of factors obviously to consider

in these cases.

switch-to-tdf**[06:44] Switch to TDF?**

Dr. Wood

So, maybe, let's steer from there to other NRTIs. Let's stay in that class of ARVs for a moment. You and I had a conversation on a different recording, where you brought up TAF and TDF [tenofovir DF] and some differences, for example, in effects on lipids. How do you, as a cardiologist and an expert in this field, consider the difference between those two drugs and the pros and cons and how does that counseling go for you?

Dr. Longenecker

It seems like there's a fair amount of evidence that TDF has a beneficial effect on lipids rather than TAF having an adverse effect. The switch from TDF to TAF, clearly, your lipids worsen, and so to me, I think it's a risk-benefit thing and there are many benefits to TAF, the renal and bone benefits potentially. And because we have so many drugs in our arsenal for cholesterol these days, I typically would be able to counter that cholesterol effect with a statin, maybe prescribing a statin certainly if someone is not on one, increasing the dose of the statin, adding ezetimibe. I mean, it is rare that we can't get someone to a cholesterol goal with everything that we have available to us these days. I think there's the weight gain issue, right, so if there are people who are switching off of INSTI [integrase strand transfer inhibitor]-TAF regimen for that reason, it may be reasonable to go back to TDF for that. But cholesterol alone? Probably not.

Dr. Wood

Interesting. So, you're not encouraging a switch to TDF or use to TDF simply for the lipid lowering effect?

Dr. Longenecker

No.

Dr. Wood

Yeah, and then there's the weight gain considerations, which are complicated and messy and we can certainly come back to, but at least in terms of lipids, cardiovascular risk, you're not seeing that as a strong reason to choose one over the other.

Dr. Longenecker

No.

Dr. Wood

That's helpful to hear.

nnrtis**[08:45] NNRTIs**

Dr. Wood

Let's go to the NNRTIs. Let's switch classes of ARVs. Let's think about the NNRTIs. Are there drugs in that class that raise your concern as an HIV cardiologist?

Dr. Longenecker

Not a lot. I think, again, it's a similar issue where everyone used to be on efavirenz, *Atripla*, and we just don't see much efavirenz anymore in the INSTI era. So, I would say that certainly any effect of efavirenz on lipids can be countered with cholesterol meds as with TAF. You know, it is important to remember efavirenz induces CYP3A4, so that blunts the effects of statins, it might decrease the effectiveness of certain statins that are metabolized through that mechanism.

I think QT prolongation with rilpivirine or other NNRTIs might be something that's relevant for certain patient populations, particularly ones that are requiring psych meds, multiple psych meds, anti-psychotics, et cetera, or methadone, for example. So, if there are interactions with other QT-prolonging agents, I would say it becomes relevant. But it's not usually me, as the cardiologist, who's recognizing. That's usually a psychiatrist or the primary HIV doc.

Dr. Wood

It's a good clinical reminder then. Again, to your point about seeing less efavirenz in clinic, I don't see it nearly as much in my practice these days. The times I do come across it, it's often driven by insurance coverage and cost issues and a need to use a generic option, but I don't come across it a lot.

If you saw someone on efavirenz and they really needed to be on it, say for those reasons, and their lipids were high, would you push for a switch off it or…

Dr. Longenecker

No.

Dr. Wood

Similar to what you've said...

Dr. Longenecker

Statin, statin-ezetimibe. I mean, I think there's just so many tools.

Dr. Wood

Treat their lipids with other tools?

Dr. Longenecker

Yeah.

Dr. Wood

Cool. Thanks, Chris.

protease-inhibitors**[10:40] Protease Inhibitors**

Dr. Wood

How about protease inhibitors (PIs)? Can you give us a rundown of how you see the boosted PIs in terms of pros and cons, in terms of lipids and cardiovascular risk?

Dr. Longenecker

The PI association with CVD risk is one of the oldest associations we have, right? In the early days, those initial publications from the D:A:D study showing that the first generation of protease inhibitors were associated with a cumulative risk, about a 10% risk per year of use, and I believe that it is a class effect. Subsequent analyses with darunavir and others showed that that was persistent.

The only drug that was not in their studies was atazanavir, which in my experience, again, we're getting back to this issue of completely falling out of favor, primarily perhaps to not being tolerated, people not liking yellow eyes from the hyperbilirubinemia. But, you know, I was in Peru the other week and saw atazanavir on the shelf. So, clearly, in some context, it is used, so if you're going to choose a PI and you cared very strongly about cardiovascular risk, I would choose atazanavir and it may be because of that hyperbilirubinemia, the antioxidant, and other sorts of effects that the hyperbilirubinemia causes that it may mitigate that increased risk.

Dr. Wood

Thanks, Chris. Maybe just to reiterate that for listeners who aren't familiar with the data. There is this unique finding with atazanavir showing a potential for reduction in ischemic cardiovascular events, right? Plausibly due to antioxidant effects of the hyperbilirubinemia.

Dr. Longenecker

I think it's more of a neutral effect rather than a perception.

Dr. Wood

Thanks, Chris. So, it doesn't have the deleterious effects of the other boosted PIs, if you will.

Dr. Longenecker

That's right.

Dr. Wood

But sounds like you don't see that as a reason to be encouraging boosted atazanavir. It comes with a lot of other issues.

Dr. Longenecker

Exactly, yeah.

Dr. Wood

Absolutely. Coming back to the same question, and again, I'm thinking about someone in clinical practice seeing someone with HIV, if someone with HIV is on a boosted PI, they have high lipids, they have other cardiovascular risk factors. Again, what does your counseling look like in terms of the importance of trying to get on a different agent, switch off the boosted PI, versus managing risk with other tools?

Dr. Longenecker

My experience has been that if they're on a boosted PI, typically darunavir or with cobicistat, it is for a good reason. It's because they don't have a lot of other options. Viral control is, at the end of the day, the most important for AIDS events, for other non-AIDS comorbidities, such as cardiovascular events. So, from my perspective, control of the HIV virus is most important and if they need the darunavir to get there, then absolutely. And so, I think it's rare that I see someone who doesn't have a good reason to be on a darunavir

regimen.

Dr. Wood

I'm glad you emphasized that point, absolutely. So let’s…. Chris, please go ahead.

Dr. Longenecker

No, I want to talk about integrase inhibitors.

integrase-inhibitors**[13:55] Integrase Inhibitors**

Dr. Wood

Hey, I think we're both heading in the same direction. So, the hot topic, the complicated, convoluted topic—that I don't think has as nice a through line as what you were talking about with abacavir—integrase inhibitors and weight gain and cardiovascular risk. What's your take?

Dr. Longenecker

We have to acknowledge the market penetration of integrase inhibitors, and practically everybody, I don't know 90+ [%] in the U.S. are on an integrase inhibitor regimen now, and it's not like we're seeing huge, massive increases in myocardial infarction because of it. So, let's step back and just acknowledge that. It's certainly been a hot topic since the 2022 publication of data from the RESPOND cohort. So, this is kind of a cohort that evolved out of D:A:D.

What the interesting finding was that there seemed to be this increased risk of cardiovascular events in that early period after initiation, zero to six months, and then it kind of tailored off to the point of really having no association with greater than 24 months of exposure. So, trying to understand what might be the mechanism there, I think a lot of people have struggled with that.

And then, last year, at CROI and then published last year, the Swiss cohort study had a nice analysis that showed really no increased risk, no signal for risk in the Swiss cohort study using a pretty high quality design. So, I was reassured by that and personally, I don't believe strongly that there is a real signal of risk. I clearly believe there's a signal of increased weight gain and some metabolic effects in some patients. We see that in the advanced trial in South Africa, particularly women in South Africa, certain portion of that group gained a lot of weight on dolutegravir and TAF. So, I think that's real and we can address that, but I think we can address it again with some of the same things. We have lots of good drugs in our arsenal these days to tackle weight gain and reduce cardiovascular risk while we're at it. Same with diabetes or glucose intolerance, the GLP-1 agonists, for example, SGLT-2 inhibitors. Then in the lipid space, I've already mentioned it and we've talked about it before, but again, clearly so many different drugs to reduce CVD risk that I think in my clinical practice, we're pretty easily able to get ahold of those sorts of complications when we encounter them.

Dr. Wood

Thanks, Chris. It sounds like overall, if I can summarize, it sounds like you are not convinced that integrase inhibitors increase cardiovascular risks. The very well done Swiss cohort study was very reassuring, I think reassured a lot of us, and I can see you agreeing to that, and you do not see cardiovascular risk as a reason to encourage people to switch off integrase inhibitors.

Dr. Longenecker

Yeah, I do not.

Dr. Wood

Yeah, I don't either and I guess I wanted to emphasize that because after the RESPOND publication, I think it was easy to have a knee-jerk reaction of, 'Oh, risk goes up and we should switch and we should get everyone on different classes,' but the data is messy and cohort studies have issues with confounders and I was really glad to see follow-up in the Swiss cohort after that.

key-take-home-messages**[17:20] Key Take-Home Messages**

Dr. Wood

So, maybe you could summarize for us your overall take for listeners and individuals who are helping people with HIV optimize their ART and also optimize their cardiovascular risk factors. What would be your biggest take-home message here?

Dr. Longenecker

I think the take home-message is viral suppression is the number one priority and patient preference to achieve that outcome. Many patients have different things that they care about. Some really want to limit their pill burden to one pill once a day. Others really care about their bone health and kidney health, there are insurance issues, weight gain and other metabolic complications for some people. So, I think just working with patients to find a regimen that works for them to control the virus is first and foremost, and then we think about cardiovascular risk after that.

So, I think it's very different than when I first started my clinic 10 years ago, when I did really think a lot more about specific antiretroviral drugs and drug classes and how that affected risk. I think nowadays, we're turning our attention more towards making sure, number one, that we are getting people on statins that we know work to reduce cardiovascular events, that we're treating blood pressure and treating blood pressure to goal, that we're treating lipids to goal, and considering aspirin in certain situations, stopping smoking. I mean, there are just so many other priorities that the antiretroviral drug regimen is probably not the leading thing from a cardiovascular prevention standpoint.

closing**[18:53] Closing**

Dr. Wood

Chris, I thought this was incredibly helpful and clinically relevant. We are going to have another conversation about aspirin for primary prevention and I look forward to that, but for now, I want to thank you. This was excellent, such a useful discussion about cardiovascular side effects of antiretroviral therapy. Thank you so much.

Dr. Longenecker

You're welcome. It was a pleasure. Thanks, Brian.

credits**[19:16] Credits**

Transcripts and references for this podcast can be found on our website, the National HIV Curriculum at www.hiv.uw.edu. The production of this National HIV Curriculum podcast was supported by Grant U10HA32104 from the Health Resources and Services Administration of the U.S. Department of Health and Human Services. Its contents are solely the responsibility of the University of Washington IDEA program and do not necessarily represent the official views of HRSA or HHS.

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