Expert Interviews

National HIV Curriculum Podcast

REPRIEVE Statin Trial: Why is It Important?

February 6, 2024

Season 1, Episode 3

Dr. Chris Longenecker, a University of Washington Associate Professor of Medicine, discusses the REPRIEVE trial design and clinical practice implications with National HIV Curriculum Podcast Lead Editor Dr. Brian Wood.

Topics:

- CVD and HIV
- cardiovascular disease
- statin therapy

Chris Longenecker, MD
Director, Global Cardiovascular Health Program
Associate Professor of Medicine
School of Medicine and Dept. of Global Health
University of Washington

Disclosures

Disclosures for Chris Longenecker, MD
Advisory Board Member: Theratechnologies

Brian R. Wood, MD
Professor of Medicine
Division of Allergy & Infectious Diseases
University of Washington

Disclosures

Disclosures for Brian R. Wood, MD
None

Transcript

Read along with the audio or jump to a particular chapter.

In this episode:

intro--background**[00:00] Intro & Background**

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.

By way of background, we know 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, but the optimal strategies for primary prevention of such events remains controversial. Recently, the first large randomized control trial of a statin versus placebo for persons with HIV limited to those with low-to-moderate estimated cardiovascular risk was completed. Findings of the study, called REPRIEVE, have garnered much attention, and I'm really looking forward to talking with an expert about this trial today.

I'm really honored to welcome Dr. Chris Longenecker to discuss the trial and discuss the clinical implications. Dr. Longenecker is Associate Professor of Medicine in the Division of Cardiology and the Department of Global Health here at University of Washington. He's the inaugural director of the Global Cardiovascular Health Program here. He is also director of the HIV cardiology clinic at our local Ryan White-funded HIV primary care clinic, and he is a renowned researcher on mechanisms and prevention of cardiovascular disease (CVD) for people living with HIV. Chris, welcome.

Dr. Longenecker

Thank you so much for inviting me. Pleasure to be here.

importance-reprieve**[01:37] Importance of REPRIEVE**

Dr. Wood

I'm really honored to have you, and really looking forward to discussing this trial, which has made a lot of headlines and we'll talk about why it's garnered so much attention and your thoughts about it. But maybe to start, I could just ask you, Chris, why you think this trial was important to conduct. Maybe you could give us your perspective on why primary prevention of cardiovascular events for persons with HIV is such an important topic to focus on.

Dr. Longenecker

Yeah. I think, first and foremost, it's about awareness. It's about making the treating HIV clinician in the field aware that cardiovascular disease is an issue, and randomized controlled trials (RCTs) are the kind of data that people really respect, and so having an RCT specifically in this population is valuable for raising awareness in the field. For HIV care, we're very familiar with the HIV treatment cascade and getting people into care, retained in care, on antiretroviral therapy (ART), and getting them to take their ART as prescribed in order to achieve suppression of the virus in the blood. But I think now it's time, since we have so many of our patients suppressed on ART, to think about extending that HIV treatment cascade for the prevention of non-AIDS comorbidities. Things like cardiovascular disease, but also cancer prevention, and things we won't talk about today. But again, I come back to that, just raising awareness amongst people treating this population in the field, that this is an important issue.

Dr. Wood

Thanks, Chris, for making that point about raising awareness. We could certainly talk for a long time about the risk of cardiovascular disease and cardiovascular events in people with HIV, and there's a lot of data and a lot written about that. But today, I'm really going to focus in on the REPRIEVE trial, and what you think clinicians should take from that, so let's just dive right into that.

trial-design**[03:36] Trial Design**

Dr. Wood

Let's talk about REPRIEVE specifically. We'll start with the design and then talk about who was in the trial, and the results, and the major findings. So, to begin talking about REPRIEVE, let's talk about the design. What do you think are the major take-home points about the way this trial was planned, and designed, and conducted?

Dr. Longenecker

Yeah, and I look forward to jumping right in. I just want to make one more point on that first question, which is to say that I think guidelines committees also like RCTs, so it's nice to have randomized trial data to give a Class I recommendation for something. And so I think there, again, and the more you have things in the guidelines, the more they will be taken up into practice, and ultimately, that's what's important. I think there's another unique piece of this trial, which is that there were a lot of different substudies and opportunities to explore mechanisms by which statins prevent cardiovascular events in people with HIV as a model for inflammatory heart disease in general, so I think that adds a lot of value to our knowledge, but what there wasn't so much of is having implementation science substudies.

It would've been nice to have more implementation science embedded within the trial to say, "Well, once we've proved this works, how can we get clinicians to actually prescribe it?" so I think that's what I want to come back to also later in this podcast. But turning to the design of REPRIEVE, this was a huge trial of nearly 8,000 people, and I say huge, certainly huge for HIV in the cardiovascular disease prevention space. We're maybe used to this sort of thing with trials of sometimes tens of thousands of patients, but this is really unique for cardiovascular disease study within this population of people with HIV. Again, randomized one-to-one to placebo or to pitavastatin, and we can talk about choice of pitavastatin, and followed for several years for major adverse cardiovascular events, so that's kind of the overall design.

Dr. Wood

Yeah. I appreciate all those points, Chris, including about the importance of RCTs, and specifically the design of this RCT, and a trial of 8,000 people with HIV is really, you know, takes a huge amount of effort, and I know that there was a lot of anticipation to see the results of this trial.

global-scope--pitavastatin**[06:10] Global Scope & Pitavastatin**

Dr. Wood

One aspect of this trial is, it was conducted all over the world, and I know you do a lot of research and a lot of focus on cardiovascular disease around the world, included in resource-limited settings, so I'm curious to ask you a bit about that part of this trial and then maybe we can come back to that question about why pitavastatin was chosen. I know that's a common question asked about the trial.

Dr. Longenecker

So I definitely think the global nature of the trial is important. There were a substantial, about over a third of participants, who were from Latin America, Southeast Asia, South Asia, and even Sub-Saharan Africa, and we'll come back to that, so that's important. But as we'll see, I think you'll find that the vast majority of the atherosclerotic cardiovascular (ASCVD) events occurred within the high-income regions, and that's also

important. But in regards to pitavastatin, that was chosen because there are no drug interactions with boosted antiretroviral therapy, and so an important consideration, certainly when this trial was designed several years ago, but as we know, the use of boosted ART is on the decline as we have unboosted integrase inhibitor-based regimens now, which are most common.

Nonetheless, you can feel comfortable prescribing pitavastatin, that there won't be interactions. It is a moderate-intensity statin, just to make that point. It does not lower LDL cholesterol, as well as atorvastatin or rosuvastatin, which are high-intensity statins, and so for people with established atherosclerotic cardiovascular disease, I think we need to make sure we're giving them the state-of-the-art, which is high-intensity statin. And so, and additionally, the drug company provided the medicine for the trial, so I think that's another, certainly, a logistical pragmatic consideration when you're designing a trial.

Dr. Wood

Thanks, Chris. At the end, I imagine we may come back to implications and how much we can extrapolate to use of other statins, but that is interesting to hear why pitavastatin was chosen and utilized.

inclusion-criteria**[08:16] Inclusion Criteria**

Dr. Wood

Maybe we could talk about the inclusion criteria a little bit because I think that's an interesting piece of the puzzle here or an interesting area to focus on with this trial because I know that individuals were enrolled based on cardiovascular risk and LDL parameters. Maybe you could take us through that a little bit and give us your opinion and perspective on why individuals within these specific parameters were enrolled.

Dr. Longenecker

The idea of the trial was that we wanted a trial where we would be looking at a population that did not already have an indication for a statin. The idea was to enroll people with an ASCVD risk score that was low. The entry criteria were modified over the first few years of the trial in part, I think, to enrich the population with a little bit more events. I'm not sure if the DSMB [Data and Safety Monitoring Board] noticed that there were few events happening, or whatever the reason was, but the criteria were expanded to eventually include participants with ASCVD risk scores above 7.5% and all the way up to 15% if they had LDL cholesterol that was not particularly elevated. So if you were less than 7.5%, 10-year risk, you had to have an LDL cholesterol less than 190. Between 7.5 and 10, your LDL had to be less than 160, and between 10 and 15%, your LDL had to be less than 130.

I think many of us would've said, "We treat many patients in those risk categories and recommend statins for patients in those risk categories, even at lower LDL cholesterols," but that was the criteria that the trial leadership landed on. I'll make a point, too, that people with diabetes were excluded unless their LDL was really low, given the clear recommendations in the 2018 guidelines in particular, and even 2013 guidelines, that people with diabetes should be treated with a statin.

Dr. Wood

Perfect. Thanks, Chris, for taking us through the inclusion criteria. I think it's important as we get to results to think about who enrolled. Any other points about the design of the trial you want to emphasize for listeners?

Dr. Longenecker

Yeah, and again, just that it was, the age group was 40 to 75 because that's where the 10-year ASCV risk calculator works and is targeted to that population, so this is not for people younger than 40, but we can talk about the implications of the trial for that age group later on.

major-findings**[10:50] Major Findings**

Dr. Wood

Let's just turn to results. Let's turn to the major findings and your impressions of what clinicians should take away from them, so could you talk us through the principle findings?

Dr. Longenecker

Yeah, absolutely. I think the high-level finding is that pitavastatin, compared to placebo, reduces the overall risk of major adverse cardiovascular events by 35%, and again, defined as a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, TIA [transient ischemic attack], peripheral arterial ischemia, revascularization, or death from an undetermined cause. So a pretty inclusive definition, but pretty standard for what we call MACE or Major Adverse Cardiovascular Events, and that notably is a significant reduction. For the amount of LDL lowering seen in the study, it's pretty impressive that we see that amount of reduction in cardiovascular events.

Dr. Wood

Let's dig into that a bit more. So, a 35% reduction in major adverse cardiovascular events comparing pitavastatin to placebo. That sounds pretty dramatic, but does that surprise you? Do you think that is dramatic? Do you think that's expected? What's your impression of those results? What's your take home?

Dr. Longenecker

So I've seen this trial presented a couple of different times since the results came out. One figure that the trial leadership has liked to show is a meta-regression of cholesterol-lowering trials over the last couple decades, showing that the reduction in major adverse cardiovascular events is related, is correlated certainly, with the reduction in LDL cholesterol, but there are some studies that are above the line, so to speak, where the reduction in clinical events kind of exceeds or is proportionately higher than the reduction in LDL cholesterol. Studies like the JUPITER study, for example, which was a trial of rosuvastatin versus placebo for people who also had evidence of chronic inflammation as evidenced by a high hsCRP [high-sensitivity C-reactive protein] level, so there's been a lot of comparison between REPRIEVE and JUPITER in that HIV is maybe a model of chronic inflammation, and similar to JUPITER, the effect on cardiovascular outcomes was greater than you would be expected to see with that given amount of LDL reduction.

Dr. Wood

Does that surprise you that the reduction of events exceeded expectations based on reductions in LDL? I'm thinking back to a prior trial as well that I know you were involved in, SATURN-HIV, and some of the findings, which I've heard you discuss previously. How do you put this together, and how surprising versus expected do you think that result is?

Dr. Longenecker

Great question. And so, personally, I don't think it's surprising. I think that we had evidence that statins are likely to have beneficial effects in people with HIV. Steve Grinspoon and his group at MGH [Massachusetts General Hospital] also published a study of atorvastatin around the same time, and so there was some evidence that statins may have some anti-inflammatory effect as well. But just in general, the effect size wasn't out of the realm of what I would expect, even if we kind of throw all the issues of inflammation aside and just think about statins in general. I expected statins to work in people with HIV. I expect statins to work in people with rheumatoid arthritis, and psoriasis, and cancer, and other conditions. I don't think we necessarily need to do a placebo-controlled trial in all those other populations to prove that, and I think that this, the REPRIEVE trial, will show people that this is a population that clearly benefits, even if the magnitude

of the effect is higher than expected or what we might've expected.

impact-on-clinical-practice**[15:05] Impact on Clinical Practice**

Dr. Wood

So, coming back, I'm thinking about the inclusion criteria you were going through and individuals enrolled into this trial with an estimated cardiovascular risk under 15% with certain LDL parameters as you outlined. So, what should clinicians take from this? Should this be practice changing? Really, should we be offering everyone a statin? How are you interpreting this for your clinical practice when you're sitting with a patient, looking at their cholesterol, and talking about prevention of cardiovascular disease? Thinking about each individual, how do you see these results, and are they changing your practice?

Dr. Longenecker

Yeah, so they did a subgroup analysis looking at the different categories of ASCVD risk, and what they showed is that, in general, there's a pretty consistent effect across subgroups of ASCVD risk. Across a lot of other subgroups, by the way. Men and women, region of the world, et cetera. But what's also shown in that forest plot of the different subgroups is that the relative risk reduction is similar, but the absolute risk reduction is very different because the absolute risk is different in these categories, and the vast majority of the events happened in people who had an ASCVD risk score greater than 5%.

And so the magnitude of absolute risk reduction is going to be greatest in those groups, and thus the number needed to treat is going to be smaller. And so what I think you'll find as different societies work through how to incorporate this into clinical guidelines is, I think personally, it's unlikely that we were ever going to recommend routine statin use in people with an ASCVD risk score less than 5%. Even though they were included in this trial, their event rates were really quite low and similar to what we would predict in the general population, so I think it's really in that higher 5 to 10% and greater than 10% group that we want to target our implementation of statin use. And so, who knows what guidelines committees will eventually say, but that's my prediction.

Dr. Wood

Thanks, Chris. So, translating this into a message for clinicians, seeing patients who might have an estimated ASCVD risk score of, let's say, 5%, what do you think clinicians should take from this trial?

Dr. Longenecker

I think clinicians should try to incorporate, as much as they can, into their routine clinical practice, some sort of measure of ASCVD risk measurement. If someone falls into the category of having a 10-year risk greater than 5%, there's strong evidence now to suggest that both the relative risk reduction and absolute risk reduction are clinically meaningful for this group, and you should at least have a patient-centered discussion about starting a statin. Many patients will say, "I don't want to start a statin," so what do you do then? And we can talk more about that some other time perhaps, but at least you're initiating that conversation with patients because I think that the benefit clearly does outweigh the risk.

We didn't really talk about risk, but important to note. People think about diabetes and statin myalgias, and we saw those in REPRIEVE, but not at any rate that's different than what we've seen in other studies, such as the JUPITER study of rosuvastatin, which really showed that there is an increased risk of diabetes, particularly with higher dose statins. And we saw an increased risk of diabetes, but again, not out of the realm of what was expected, and similarly, with muscle symptoms, not out of the realm of what would be expected for a statin trial.

key-take-home-messages**[18.53] Key Take-Home Messages**

Dr. Wood

So let's try to wrap up here and come back to strengths and limitations of the study. You hinted a bit at the beginning of what you see as some of the limitations, and then the big take-home messages and how much clinicians can extrapolate from this to other statins like atorvastatin, rosuvastatin you mentioned, so if you could bring us back to what you see as strengths, limitations, and most important, messages.

Dr. Longenecker

Yeah, the strengths, I mean, include just obviously the large nature of this study, the randomized trial design, inclusion of lots of diverse people from all over the world, and ultimately, a lot of the mechanistic substudies will teach us a lot about the mechanisms, so those are the strengths. I think the limitations are that this issue of just absolute versus relative risk reduction, and just helping make sure that when we talk about this trial for treating clinicians that we think about absolute risk reduction and absolute risk. So what are the populations that are at highest risk? Those are the populations we want to reach out to first for implementation, and there's really low-hanging fruit. I assure you, there are many people in our primary HIV care practices with ASCVD risk scores greater than 20% who have never had a statin conversation with their provider, so we need to have those conversations first with those higher-risk people before we start thinking about implementing this in really low-risk people.

Dr. Wood

That is such a key take-home message. I'm really glad you emphasized that at the end. I'll ask one final question because I hear it get asked a lot. If pitavastatin comes off patent, or when it comes off patent, are you taking this study to mean we should be prescribing that, or are you extrapolating this to, let's say, atorvastatin, rosuvastatin? The statins we prescribe in practice right now?

Dr. Longenecker

Sorry. Yeah, I forgot to mention that earlier, and absolutely, I think this is a statin class effect, and in my clinical practice, I use a lot of atorvastatin, rosuvastatin because they're generic. It's just a lower barrier to care, so I think that people should feel comfortable prescribing atorvastatin and rosuvastatin, looking out for drug interactions in certain situations. But yeah, and I look forward to talking more about the other statins, non-statin therapies, and other ways of reducing cholesterol as well to reduce cardiovascular disease in our population.

closing**[21:20] Closing**

Dr. Wood

Chris, thanks for this excellent discussion about the REPRIEVE trial. How it may impact our practice and primary prevention strategies in our HIV clinical work. Thank you so much for your time.

Dr. Longenecker

Thank you, Brian. It was a pleasure.

credits**[21:38] 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.