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Expert Interviews

National HIV Curriculum Podcast

Pharmacologic Management of Hyperlipidemia

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Dr. Chris Longenecker, a University of Washington Associate Professor of Medicine, and National HIV Curriculum Podcast Lead Editor Dr. Brian Wood discuss treatment of hyperlipidemia for individuals with HIV (PWH), with a focus on tools to estimate cardiovascular disease risk, selecting lipid-lowering agents, and key drug-drug interactions, as well as managing adverse effects or nonresponse to initial therapy.

Topics:

- CVD and HIV
- cardiovascular disease
- ASCVD
- statin hyperlipidemia

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Disclosures

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Transcript

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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.

As background, individuals with HIV have higher likelihood of developing cardiovascular disease (CVD) and experiencing major adverse cardiovascular events including myocardial infarction (MI), stroke, and others as compared to individuals without HIV. Management of elevated lipid levels is an important part of cardiovascular disease prevention and is a critical aspect of primary care for persons with HIV. But questions often arise in clinic, and the optimal management is controversial. So, I'm really looking forward to today's conversation.

I'm honored to welcome Dr. Chris Longenecker to discuss this issue and give his expert insights. 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, director of the HIV cardiology clinic here at our local Ryan White-funded HIV primary care clinic, and he is a renowned researcher on mechanisms and prevention of cardiovascular disease for people living with HIV. Chris, welcome.

Dr. Longenecker

Thank you so much, Brian. It's a pleasure to be here. Looking forward to the discussion.

Dr. Wood

It's an honor to have you.

considerations-lipid-lowering-meds**[01:25] Considerations for Lipid-Lowering Meds**

Dr. Wood

So, let's discuss indications for pharmacologic therapy to address hyperlipidemia. Let me just start with this question: What factors do you consider when thinking about whether a person would benefit from medications to lower their lipids?

Dr. Longenecker

Absolutely. I think that the first order of business is just understanding this idea of absolute risk, and how do we estimate someone's absolute risk of having an atherosclerotic cardiovascular disease (ASCVD) event. That's what we're primarily targeting and trying to treat by reducing high cholesterol. And so there are various methods out there, risk calculators that take the main key traditional risk factors into account to estimate a global risk. And so the most well known of these certainly in the United States context is the 10-year ASCVD risk calculator, known as the Pooled Cohort Equations endorsed by the American College of Cardiology and the American Heart Association. These were originally developed in 2013 and then further

endorsed by the 2018 cholesterol guidelines.

But I'll make a note that there are new equations out there. For some of your listeners, they may be aware. The American Heart Association has now announced the PREVENT calculator, the PREVENT equations. So, I think you'll start seeing those come into routine clinical use. These new equations importantly incorporate BMI and estimated GFR [glomerular filtration rate] and take a view of cardiovascular disease as inclusive of cardiometabolic disease in general. And that's really, really important I think in our current era.

What you won't see in the new equations is a race term. So, we're getting away from using race, recognizing that race is a social construct that's really that's not what is predictive of risk. It's rather more likely social determinants of health and other things that are associated with risk. And so I think these new PREVENT equations also can incorporate social determinants of health, and you'll see if you read the full document that those things will be incorporated. And so I think the future of risk prediction is bright. We'll be getting away from race-based risk prediction and moving towards other things like using social determinants of health.

But, for now, in my clinical practice and because super easy in Epic to just hit ".ASCVD risk," that's what I use. And I'll say, it's relatively well calibrated for people with HIV. In general, those equations over-predict risk in the general population. So if people with HIV have a slightly higher risk because of their chronic HIV infection, it actually turns out the risk prediction is pretty good. And if you look at the REPRIEVE trial, which had a placebo group, rigorously adjudicated ASCVD events, you can see that for men in particular, it's a pretty good risk calculator. The risk tracks pretty good with the ASCVD risk. For women interestingly, that it may still under-predict risk. So just keeping in mind that for women with HIV, they may have a higher HIV-associated risk. And so keeping that in mind and having maybe a lower risk threshold to think about lipid-lowering therapies in women versus men.

Dr. Wood

Chris, thanks for all of that. A number of really important points there.

hiv-ascvd-risk**[04:59] HIV and ASCVD Risk**

Dr. Wood

With the old Cohort equation, not sure about the PREVENT calculators, HIV has been described as a risk enhancer. I'm wondering if you can explain what that means and how you incorporate the presence of HIV into your estimation of risk when you're looking at those numbers.

Dr. Longenecker

I think most of your listeners will be familiar that there's now a huge literature of the epidemiology suggesting HIV is associated with maybe a 50%, 50% to 100% increased risk, so 1.5- to 2-fold increased risk of cardiovascular events. So what do you do with that? Do you just multiply your 10-year ASCVD risk by 1.5? Well, no, I don't do that because as I just said, it tends to predict well in men because it's actually under-predicting risk in the general population.

So, in terms of adding HIV into the risk calculator, I don't do that. There are HIV-specific calculators out there. People may be familiar with the D:A:D risk calculator, which is based on the D:A:D study. Again, that epidemiology is starting to get a bit dated now. And so maybe that doesn't reflect true practice or true epidemiology of risk. That said, that does give you a way of quantifying the associated risk for certain types of antiretroviral therapies such as protease inhibitors or abacavir. So some people may find that helpful. Going back to your question, I think that at any given level of risk, the fact that someone has HIV is just one more factor to kind of help inform the doctor-patient relationship and the patient-centered, patient-informed decision-making. And so I think along with other factors we can talk about.

other-markers**[06:46] Other Markers**

Dr. Wood

So, how do you incorporate other markers, whether they're blood markers or coronary artery calcium scores or other clinical factors?

Dr. Longenecker

A few markers that are out there. People have heard about lipoprotein (a), another really important biomarker for atherosclerotic cardiovascular disease events. And I think it should be checked once in everyone's lifetime. It's genetically determined. And if you have a high Lp(a), there are drugs that are being developed that will specifically target that. In the current era, we simply generally are just a little bit more aggressive with LDL lowering in that population. ApoB particle concentration is another thing that some people use. I don't tend to check particle concentration, although when you think about atherogenic lipids, that's what matters most is the number of particles that are out there circulating. But there's actually a really good surrogate measure on your normal lipid panel that you can use instead of ApoB, and that's the non-HDL cholesterol. So it's your total cholesterol minus your HDL. And that's what I tend to use when I'm thinking about targets of lipid lowering and thresholds to start lipid therapies.

Calcium score is another really important imaging biomarker that I've used a lot in the past in part because where I was in Cleveland, it was free to get a calcium score. Now in Washington State, there are still not many insurance companies that will pay for it. But if it can be paid for or if a patient is willing to pay out of pocket, in some places it can be low, as low as $100, $100 to $300. It is a two-way recommendation in the 2018 cholesterol guidelines to do a calcium score if someone is on the fence. So, if someone can't decide whether they want to start a statin, and I think it would be valuable, getting a calcium score can really reclassify the risk.

If your score is zero in particular, we talk about the power of zero. If you have no calcium in your coronary arteries, your risk of a 10-year atherosclerotic cardiovascular event is quite low. And I think it's safe to delay statin initiation if you're really hesitant. Whereas, if the calcium score is quite high and there are risk calculators that take into account calcium score, in particular the MESA calcium score calculator will incorporate calcium score, and that can really increase your risks. So take someone from a 7.5% risk to a 15% or 20% risk, and maybe that's enough to convince them to take a statin.

Dr. Wood

Super interesting and really clinically relevant. Thank you for that, Chris.

Dr. Wood

Coming back to the risk-estimating calculators, I believe they were all really designed to use above or within a certain age range, like above 45. How do you have this conversation with someone who's let's say below 45, below 40 and has an elevated LDL when you're in clinic?

Dr. Longenecker

So, as a reminder, the 2018 guidelines do recommend treatment of LDL cholesterol if it's greater than 190 no matter what your cholesterol. And many of these patients have familial hypercholesterolemia, heterozygous familial ([He]FH). So family history is very relevant for younger people less than 40 years. And so if that is someone's only risk factor and you're going to try to get them to age 95 or 100, you know it's maybe reasonable to start them on an LDL cholesterol-lowering agent at a younger age. So, I personally started a statin before I was age 40. So there are good reasons to do it, but it's an individualized decision.

Dr. Wood

Thanks for sharing that.

changing-art**[10:32] Changing ART?**

Dr. Wood

So, before we talk about the specific lipid-lowering agents, I'm curious to ask you, are there instances in your clinical practice these days where in order to help with hyperlipidemia you recommend a change of ART?

Dr. Longenecker

So great question, and this is not a podcast on the lipid effects of ART, but as we all know, certain ART, we think of TAF [tenofovir alafenamide] for example, may have a different effect on lipids compared to TDF [tenofovir DF]. Or maybe its TDF actually has a beneficial effect as we know on lipids. And so what happens when you make that switch from TDF to TAF, and your lipids kind of climb a little bit into more of a range where you think treatment is necessary, then my recommendation is start a statin. Not necessarily that you need to switch the ART. Unless it's a really, really difficult to control situation, then you may occasionally. Now it's a different question if you're on an ART regimen that's associated with an increased risk of myocardial infarction and perhaps you've had multiple MIs in the past. Then I might revisit that question with a treating HIV provider if I'm the cardiologist consulting there, but not usually just to address lipids.

statin-options**[11:54] Statin Options**

Dr. Wood

Thanks Chris. And let's turn to the agents. What's your first agent of choice? How are you considering the options, and where do you start?

Dr. Longenecker

Clearly statins are our first line for treatment of high cholesterol. This was true before the publication of REPRIEVE, but absolutely true now that the REPRIEVE trial is out there. There's just a lot more awareness of statins, and I think the effect is seen in REPRIEVE is a class effect, so it doesn't matter what your initial choice is. I tend to use atorvastatin and rosuvastatin because that's what I'm comfortable with. I'm a cardiologist. I like to see low LDLs, so I want a high-intensity statin. Now you have to worry about drug interactions with both atorvastatin or rosuvastatin. For atorvastatin, if there is a cobicistat or protease inhibitor interaction, I start low and go slow, typically up to a max dose of atorvastatin of 20, very rarely 40 milligrams if tolerated. But rosuvastatin also can be very effective at lowering LDL in those populations. I think if you have someone with established ASCVD, it's really important you get them on a high-intensity statin.

Dr. Wood

Chris, in your practice, are you ever reaching for other statins, pravastatin, simvastatin, lovastatin, pitavastatin?

Dr. Longenecker

Honestly, no. I can't remember the last time I prescribed pravastatin. I think back when I was in Cleveland, I had one patient who really tried many different statins, and pravastatin was the only statin she could tolerate. And so we did use pravastatin in her case, but any statin is better than no statin. And in terms of statin myalgias, if people are really having trouble tolerating, you need to cycle through other statins and challenge with maybe a lower-intensity statin, maybe trying a really low dose of a long-acting statin like rosuvastatin

once a week or three times a week at a dose of 5 mg. Just trying as much as possible and not calling someone statin-intolerant until you've gone through all of that. But we have options now for people who are statin-intolerant. So we'll talk about those.

Dr. Wood

And we'll talk about that. First, I want to ask you, are there ever instances in which you recommend dual therapy to lipid-lowering agents at the start, or do you always start with one and add later if needed?

Dr. Longenecker

If someone has never been on anything, I just start a statin, right. So there is a variability in the LDL response to statin. Some patients have a very high reduction and then others less so. So you have to see what the response will be and whether you can get someone to go if that's how you practice. And if you need additional agents later, then you add them.

Dr. Wood

I see. Thank you for that.

monitoring-efficacy**[14:38] Monitoring Efficacy**

Dr. Wood

So honing in on that, how are you monitoring and what are your goals? And that'll lead us into talking about when you decide to add additional agents.

Dr. Longenecker

So typically you'll see an effect of the statin within a few weeks. So you can recheck in four to six weeks if you want. It kind of depends on the cadence of your usual meeting with the patient or how often you're seeing them in clinic. But waiting three months is not unreasonable as well. So you start a statin, and then you follow-up in a certain period of time, and you see if the LDL reduction is what you would expect. And with a high-dose statin, you're going to hope for about 50% reduction in your LDL cholesterol. And if you can get that on a statin, great. And particularly if you can get to an LDL goal, which for most of my patients who are people living with HIV, often with comorbidities, that's typically an LDL cholesterol less than 100 in my mind. That's a non-HDL cholesterol of less than 130. Whereas, if you have established disease, I'm shooting for at least an LDL of 70 if not an LDL lower than 50, which would be recommended based on the European guidelines for example.

non-statin-options**[15:50] Non-Statin Options**

Dr. Wood

Let's take the instance of a person who's taking their statin, tolerating it, but not reaching those goals you just outlined. What's your next step?

Dr. Longenecker

Again, it also goes back to the absolute risk reduction. So, if someone is very high risk, particularly if it's a secondary prevention case where they've had an MI, they've a stroke in the past, and you need to get them, really need to get them to goal, and the absolute risk reduction is significant because their absolute risk is high, then I reach for ezetimibe as the next step. Actually, this would be true really in anyone who needs more LDL lowering. Ezetimibe will lower your LDL cholesterol by another 20% on top of statin, and it's been

shown to reduce your risk of major adverse cardiovascular events on top of statin. That was shown in the IMPROVE-IT trial.

So, we have ezetimibe, which is cheap, super well tolerated option. So what happens then if you can't get to goal on statin and ezetimibe, that's when I think about PCSK9 inhibitors, which are injectable monoclonal antibodies of the PCSK9 protein. So this is a long story and maybe outside the scope of this podcast, but people with low PCSK9 levels were found to have low risk of cardiovascular events, and this genetic discovery led to this new drug in a very quick timeframe. And so now there are different ways of targeting this protein with monoclonal antibodies, evolocumab, and alirocumab. But now we have a new kind of drug called a small interfering RNA drug, so inclisiran can do that with an injection that's every three months and then every six months eventually, which is kind of like long-acting ART. So if you get your Cabenuva, you can get your inclisiran at the same time. And so that may be coming down the road for some patients.

And so I think there are lots of different options and there are other oral options as well. Bempedoic acid is a drug that works in the same line of action of statins, but really upstream of HMG-CoA reductase. So it targets adenosine triphosphate citrate lyase in the liver, and bempedoic acid works only in the liver because of how it's designed. It's a pro-drug that's taken up into the liver and does not get into muscle. And so what we've seen in the trials of bempedoic acid is that there are not as many muscle side effects, which is great. And it is available alone or in combination with ezetimibe, so you can get a single pill that gives you the ezetimibe combo plus the bempedoic acid. And it has been tested in combination with statins. So even though it works on the same pathway as statins to reduce production of LDL, it can be used in combination therapy. And so it provides an additional LDL reduction, and then it also seems to decrease hsCRP levels. So there may be some anti-inflammatory things. So I think bempedoic acid is a really intriguing drug, again because it's an oral drug for people who are scared of injecting. But again, still a branded drug. Cost is an issue and getting it paid for. So it's kind of unsure where it will fit in the marketplace given all these other options. But I am very, very optimistic about the future of lipid-lowering therapies. And I think in the future we'll be getting people to very low LDL levels.

You know, people on PCSK9 inhibitors can get to LDL cholesterols in less than 10, even negative values, which result from the fact that LDL is a calculated value from the lipid panel. And so sometimes you can see a negative value. And from everything we've seen so far, there doesn't seem to be any negative effects of getting cholesterol that low. And in fact, we see plaque regression in the coronary arteries. So I think, again, a very exciting time for lipid-lowering therapy in general. And at the end of the day, things like binding agents, and things that we used to use 20 years ago just really aren't going to be used in clinical practice.

Dr. Wood

Super interesting, and great to hear your perspectives on the future of lipid-lowering therapy.

statin-intolerance**[20:10] Statin Intolerance**

Dr. Wood

In that array of options you just outlined, if an individual *really* cannot tolerate a statin, what you're reaching for. And you mentioned before trying different statins, trying lower intensity, trying less frequent dosing. But if a person really cannot tolerate a statin, then what are you recommending?

Dr. Longenecker

I think you have two main options, and it's either the bempedoic acid in combination with ezetimibe or a PCSK9 inhibitor. And so at that point it's often a discussion with the patient, "Do you want a pill, or do you want an injection?" And then if the insurance company has a preference. And given how insurance companies and drug distribution and all the arrangements between insurance companies and distributors, it's just hard to predict sometimes what any given insurance company will pay for. So, whatever works, works for me. Just

getting that LDL cholesterol low.

Dr. Wood

Thanks, Chris. Yeah, absolutely. The cost and access issues can be complicated and can present barriers and are an important part of that consideration. Chris, this is so valuable. I always learn so much from you. For time, I'm going to lead us to wrap up here shortly, and we'll plan follow-up conversations around related aspects of this.

take-home-messages**[21:26] Take-Home Messages**

Dr. Wood

But maybe you could finish with what you see as the most important take home-message for clinicians and a note about additional research you'd like to see in the future. Where do you want to see this field go? You've mentioned that a little bit, but please go ahead.

Dr. Longenecker

I think it's all about implementation of guidelines. We have so many evidence-based therapies for lowering cholesterol and just so much promise, and yet in clinical practice it doesn't happen. And why is that? What are the barriers? There are patient level barriers, there are practice level and system level barriers, but there are people with ASCVD risk scores of 25% or higher who are out there who've never had a conversation with their clinician. And so how do we get those conversations to happen? How do we overcome clinical inertia? How do we get it on the radar of a primary care provider who's got 50 other things to think about, right? And when you're dealing with populations that are vulnerable, that have issues accessing care, there are many, many considerations. And I agree there are people who shouldn't be on a statin even though their ASCVD risk score is high, but we should not use that as an excuse to forget about it when there is a good indication.

Dr. Wood

Chris, that’s such an important message. We will end it there. And I just want to say thank you for your time and expertise. I look forward to follow-up conversations with you. Thank you for this excellent discussion.

Dr. Longenecker

Thank you so much, Brian. It's always fun.

credits**[23:00] Credits**

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