Expert Interviews

National HIV Curriculum Podcast

Antiretroviral Therapy (ART) and Weight Gain

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Managing weight gain with the use of newer generation HIV ART regimens is controversial. Dr. Sara Bares, a University of Nebraska Associate Professor, discusses key studies and how to counsel patients about potential impacts of initiating or switching a regimen with National HIV Curriculum Podcast Lead Editor Dr. Brian Wood.

Topics:

- ART
- NRTI
- HIV
- weight gain
- CVD and HIV

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Transcript

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

In this episode:

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introduction**[00:00] Introduction**

Dr. Brian Wood

Hello, everyone. I'm Dr. Brian Wood from the University of Washington in Seattle. Welcome to the National Interview Curriculum Podcast. This podcast is intended for health care professionals who are interested in learning more about the diagnosis, management, and prevention of HIV.

So, as background to this episode, in the modern era of HIV care, we're very fortunate to have potent antiretroviral regimens that are highly effective, in general, very well tolerated. But a very important issue that has repeatedly come up in clinic and in research in recent years is weight gain and other metabolic changes that can occur after starting or switching antiretroviral therapy (ART). Beyond the weight gain that can occur, the potential increases in long-term cardiometabolic comorbidities with certain antiretroviral classes and certain agents as compared to others, has become a topic of a lot of discussion and controversy. So, today, we are going to explore this topic. I'm honored to be joined by Dr. Sara Bares, an associate professor in the Division of Infectious Diseases at University of Nebraska Medical Center and College of Medicine. Dr. Bares trained in internal medicine and infectious diseases at the University of Chicago, and now, as faculty at University of Nebraska, dedicates her time to the care for people with HIV, to teaching students and trainees, to studying long-term complications of HIV and antiretroviral therapy and to many other efforts and pursuits. And we are very honored to have Sara with us today. Sara, welcome.

Dr. Sara Bares

Thank you so much for having me. I'm looking forward to the discussion.

Dr. Brian Wood

I'm looking forward to it as well. It's obviously a very hot topic, and so let's just dive right in.

long-term-health-outcomes**[01:36] Long-term Health Outcomes**

Let's start with what we currently know about weight gain that's associated with antiretroviral therapy and why it's become such a hot topic. And, you know, many studies are looking at this. There's a lot of clinical conversations about this. There's a lot of research about it. Maybe we can just start with why this has become so important to the field from your perspective.

Dr. Sara Bares

Yeah, I think it's incredibly important. People with HIV are living longer than ever before because ART works. As you said, it's potent. It's effective. It's well tolerated. The most utilized regimens are associated with high virologic efficacy, low rates of failure and resistance, and patients who are diagnosed with HIV linked to care and prescribed ART aren't dying of HIV, but they're facing higher rates of obesity, diabetes, cardiovascular disease than the general population. Heart disease is the leading cause of death in the U.S., and people with

HIV have two times the risk for cardiovascular diseases as those without HIV. So, I think the challenge for those of us who care for and about people with HIV is really to determine how to minimize the risks of these comorbidities so that we can improve not just the life span but also the health span of people with HIV. And really, in order to do that, we need to know whether certain regimens portend a higher risk of weight gain and other cardiometabolic complications than others.

Dr. Brian Wood

Sara, thanks so much for that. And pausing on that for a moment, I'm reflecting on how you really focused on the long-term cardiometabolic outcomes. And I want to just interject here—we're in this discussion, and a lot of the research and conversations, a lot of focus on weight and on BMI [body mass index]. And I really want to acknowledge that weight and BMI are not markers of health, that these conversations do have potential to be stigmatizing, and providers should never shame about weight. And, really, we should be focusing on well-being, acknowledging body diversity, and really focusing on what I think you just said is the long-term health outcomes, the long-term cardiometabolic comorbidities, and associated complications that could come of these things. I want to acknowledge that and maybe ask for your reflections on that as well.

Dr. Sara Bares

Yeah, I'm so glad you bring that up. I think it's really important that as we talk about in general, the health of people with HIV, that we recognize that some of the terms that we may use in a clinical setting are going to be perceived differently by different patients. And we really want to be sensitive to that and think of the repercussions that our words and our language may have.

Dr. Brian Wood

Yeah, absolutely. Thanks. Thanks, Sara, for adding that. I appreciate it, and want to come back to that and ground us in why we're focusing on this; this is really long-term health. And we'll come back to some of the reasons it is important. I don't know about you, but this has come up for me in clinical discussions around starting ART or changing ART. I mean, it does become important for individuals. And then, you know, as a whole, we're thinking about long-term health for people. So, thanks for coming back to that.

two-key-studies**[04:45] Two Key Studies**

Dr. Brian Wood

Maybe as a next discussion point, we can break this into initial ART (starting ART) for someone who's never received it before. And then later we can talk about switching ART. So, let's focus first on starting ART. Maybe you could provide some background into the data and your experience and what we know and don't know about changes in weight, BMI, and health outcomes based on different regimens for a person starting ART for the first time.

Dr. Sara Bares

I think that's a great way to think about it and break it up. In some of the first studies that really helped answer the question about weight gain with ART initiation were really enlightening. One of the ones that made a big impression on me, and I think really shed a lot of answers was a pooled study that Paul Sacks led. It was eight different randomized controlled trials of treatment-naïve people with HIV who initiated ART over a period of about 12 years up to 2015. And, what they found was that the weight gain was greater in the later trials and with the use of newer ART regimens. And then, with respect to ART class, they found that the integrase inhibitors were associated with more weight gain than both the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors [NRTIs]. They were some of the first findings, but they've been confirmed in subsequent studies.

So another example is the ADVANCE study trial, which was an open-label, randomized, controlled trial conducted in South Africa that compared a three-drug regimen of emtricitabine and dolutegravir plus either tenofovir alafenamide (or TAF) or tenofovir disoproxil fumarate (or TDF) against the local standard of care regimen, which was TDF-emtricitabine and efavirenz. And then the patients who were randomized to dolutegravir-based regimens, especially when in combination with TAF, experienced a significantly greater weight gain as compared to those who were randomized to the TDF-based regimens and to the standard of care.

Dr. Brian Wood

Thank you for summarizing those. Those were important studies. They made a lot of headlines. They, you know, I think really impacted how we think about these things when we're making clinical decisions. So, but how do you put that all together? How do you put that all together as a message for trainees, for clinicians or for counseling patients and maybe starting on thethe first piece—that pooled cohort study was, was so fascinating. And the newer studies seem to all be different than the older studies and integrase inhibitors seem to stand out. So, how do you translate that into a message for clinicians making decisions and for patients considering options for initial ART?

Dr. Sara Bares

What we need to appreciate is that as ART has become more effective, better tolerated, and more potent, that we have to acknowledge some of the potential side effects that our patients may experience and that we need to monitor for, and so, really not to undermine how incredible these medications are because really from a virologic efficacy standpoint, they're unbelievable. One of my mentors said we never would have dreamed of this 40 years ago at the beginning of the epidemic that our current first-line regimens would have efficacy rates, virologic suppression rates, of over 90% and without risk of resistance at the time of failure. It really is remarkable. And so, not to undermine that, but to acknowledge that there are some side effects that we're beginning to see emerge, particularly with these newer regimens that we need to be mindful of, that we need to counsel our patients about, and then we need to really study to determine what is the clinical significance of these side effects?

off-target-side-effects**[08:44] Off-Target Side Effects**

Dr. Brian Wood

Maybe if I can come back to one more question on that topic. I think another challenge is how much might be an inadvertent off-target side effect of the newer drugs, integrase inhibitors for example, versus some sort of side effect of the older agents that we didn't fully understand at the time and probably still don't fully understand. What do you think about that, and how do you put that together in your mind as a clear message for clinicians and for your patients?

Dr. Sara Bares

I think you've hit the nail on the head there. We have seen that these newer regimens, particularly the second-generation integrase inhibitors, dolutegravir, bictegravir, have been associated with more weight gain than the earlier-generation integrase inhibitors. And then among NRTIs, the tenofovir alafenamide, in particular, has been associated with more weight gain than the TDF, abacavir, zidovudine, other NRTIs. And, so what we don't know is whether these newer medications are contributing to weight gain or whether it's removing the suppressive effects of the older generation antiretrovirals. So, for example, when we remove TDF, we see more weight gain. When we remove efavirenz, has been noted to have more of the weight suppressive effect. So, is it that we're removing the suppressive effects of these older medications, or are these newer medications really causing leaking? We don't know yet.

Dr. Brian Wood

Thanks, Sara. And I imagine we'll get a little more into that when we talk about switching ART as well. But I do think, based on what you're saying, based on what I understand about this topic, it does make the comparison challenging. How much of this is the newer agents maybe causing some sort of off-target effects versus the older agents causing a weight suppressive factor? When you compare them in research, it becomes very difficult, I think, to interpret.

counseling-patients**[10:43] Counseling Patients**

Dr. Brian Wood

Let's come back to the clinic and let's come back to imagine ourselves sitting in front of a patient, considering the options in the guidelines, the options for initial ART. You know, I want to be clear: Guidelines in this country do clearly say that this potential for weight gain should not affect our choice of initial therapy. I'm wondering if you could take us through how that counseling goes for you about the options. So, what your thought process is, and if you agree with that point in the guidelines, if there are *ever* any clinical situations where you actually might consider maybe not choosing bictegravir or dolutegravir, for example, as initial therapy?

Dr. Sara Bares

That’s exactly right. So, all of the recommended initial regimens in the guidelines contain either dolutegravir or bictegravir, which we now have multiple studies confirming that these are associated with more weight gain. Although the guidelines acknowledge that these have been associated with greater weight gain than other regimens, they don't recommend that we alter our selection based on the potential for weight gain and I agree, for the most part, and maybe I'll explain why I hedged just a bit. You know, I think the currently recommended first-line regimens are incredibly effective. High biologic efficacy. And, again, like I mentioned earlier, it would have been beyond our wildest dreams to have imagined that they have such high efficacy rates, high barriers to resistance, but, in addition, all of our patients face a potential for weight gain, although some may be at higher risk, really everyone I see coming in to start ART is at risk for weight gain. And so, I agree that in the absence of another indication to choose an alternative regimen, I wouldn't, even if my patient has both maybe disease or a demographic-related risk factor that may put them at higher risk for weight gain. That said, I'm always willing to make an exception if I think the benefits of doing so outweigh the risks, and one of my mentors told me that the best medication for a patient is the one that they'll take. And I think, you know, reflecting back, that lesson, I think, was about cost and really the importance of keeping cost in mind and access to medication. And if you prescribe a medication for a patient, but they can't pay for it when they get to the pharmacy, they're not going to take it. I think it really also applies to this discussion that we're having today.

And so, the way I apply this in my care is I talk to every patient who's starting ART about the potential for weight gain, and I get their thoughts, just pause and ask them if they have concerns about that, if they have any questions for me. Some will take it home and go on our advice and just take the medication. But others will read the fine print, the label, really, really closely. And they may see weight gain on that. And I think so it's really important to let them know in advance. And if a patient has a strong reaction, if they express real concerns about the weight gain, I will probe more and discuss more. And if I get the sense that it will concern them enough to where they won't take the medication or whether they’ll try stopping it or taking it less, anything that could jeopardize our success rates, then I will consider an alternative regimen.

Dr. Brian Wood

Sara, thanks. I think that's very practical, very useful for clinicians, anyone doing this counseling, considering the options initially. I love that take home that the best regimen is one that a person will take, that they'll be able to adhere to, that will suppress their viral load. I mean, that really is the most critical goal here.

risk-factors**[14:34] Risk Factors**

Dr. Brian Wood

You also mentioned in there that there might be other demographic factors, clinical factors that have been associated with more weight gain with antiretroviral therapy. Maybe you could take us through that a little bit more. What factors, either in your clinical experience or in the research, have been associated?

Dr. Sara Bares

Yeah, thanks for reminding me. So, in in both clinical experience and in multiple different studies, some risk factors have certainly emerged as being more associated with weight gain. From a disease standpoint, they're somewhat intuitive in that those with more advanced disease or markers of more advanced disease, for example, higher viral loads and lower CD4 counts, are associated with more weight gain. And I think those of us who care for patients every day in the clinic can understand that intuitively, we see patients with advanced disease come in looking frail and thin, and so it's not surprising that they are at higher risk for weight gain. When we see that weight gain, we celebrate it, you know, they feel healthy again and they look healthy. But some of the other demographic risk factors that have emerged are less intuitive and perhaps a little harder to wrap our minds around. And so, some of those have been, for example, Black race, the Hispanic ethnicity, and then the female sex. So all of those, for reasons that we don't fully understand and are likely multifactorial, have emerged as factors that are more associated with weight gain.

Dr. Brian Wood

Thanks so much, Sara, for outlining that for us. I think there's a couple of things we're getting at here, and one is that there are still a lot of outstanding questions about this. And I don't know about you, but when I sit with a patient in clinic, I go through similar counseling. It's helpful to hear what you go through. And I also find it very difficult to predict which patients are going to develop excess weight gain after their initial ART. Like you said, part of that weight gain is healthy, and we, we celebrate it; and it’s a sign of the virus suppressing and a person returning to health. And I also want to be clear, not everyone gains excess weight and develops comorbidities and complications. So, I think that counseling, as you said, you go through and then monitoring and individualizing and helping an individual really choose what's right for them is so key.

long-term-comorbidities**[16:53] Long-Term Comorbidities**

Dr. Brian Wood

Maybe we can come back to what you were getting at the beginning that really the importance of this is the long-term comorbidities and health outcomes. And maybe as a follow up question, I can ask you, what do we know based on clinical experience, based on research, what do we know not just about weight and BMI change but about long-term health outcomes? Is what we're discussing, does it really lead to differences in things like diabetes and metabolic syndrome and hypertension and cardiovascular events developing over time?

Dr. Sara Bares

That's the key question. So, is this weight gain clinically important? It may be statistically significant in studies, but is it clinically significant? And I think it's one of the harder questions to answer because in retrospective studies, or observational studies, they're full of confounding, and prospective studies with cardiometabolic endpoints take massive amounts of resources like the REPRIEVE [Randomized Trial to Prevent Vascular Events in HIV] trial, which was really a landmark trial. And we're so grateful to have answers to that in the field, but really took, you know, an all-star team and tremendous resources. So these are harder questions to answer, but there's beginning to be some emerging data. I just worked on a study to help answer this question just a tiny bit with colleagues from the ACTG [AIDS Clinical Trials Group]. And the findings were really both, I would say, fascinating and humbling because we discovered that the weight gain in those first 48 weeks of ART. So that first year, we really often celebrate this weight gain and thought that a lot of that

early weight gain represented a return to health. It's actually associated with numerous cardiometabolic outcomes. And so participants who experienced more than 10% weight gain in that time when compared to those who either lost 5% of their weight or gained only 5% of their weight had a twofold increased risk of diabetes, metabolic syndrome, and a 50% increased risk of cardiometabolic outcomes. So, I think, humbling because how do we prevent that weight gain? You know, should we really be counseling patients when we spend so much of that first visit telling patients about the importance of their ART and how their life expectancy can be on par with those without HIV if they are able to take that medication every day and control the viral load. That's *the* most important outcome. But yet, how much should we be focusing on these other side effects that may occur, that probably will occur, knowing now that they may well be clinically significant.

cardiometabolic-outcomes-monitoring**[19:38] Cardiometabolic Outcomes Monitoring**

Dr. Brian Wood

Thank you for that. So I think what I'm hearing and what I'm getting at is that this is a really key piece of the initial counseling. For the most part, it sounds like you don't alter your choice of ART based on this potential, but you do alert people to it. You do have a conversation about it, and you do, it sounds like, a monitor for some of these comorbidities and complications. And maybe we can get into what what you do if that occurs. But what does that monitoring look like for you? What are the follow-up discussions and the monitoring look like in your clinic?

Dr. Sara Bares

Yeah, that's exactly right. So the main follow-up that we do when it comes to outside of those biologic endpoints, and just in clinic at least, are just keeping a really close eye on weight as patients are initiating ART and coming in for their more frequent follow-up early on after starting ART. If I start to see a really steep curve, a steep increase in the weight gain, I quickly counsel patients and at least help them recognize it. Some of them report that their appetite becomes voracious and if they can at least recognize that and acknowledge that, that's important. We talk about access to food and access to healthy food, which is, I think, undertaught and underappreciated that the role of what type of food patients are eating, access to places where they can be physically active is important, especially in places like Omaha where in the winter there are very few places to be physically active. And so I think the diet and the lifestyle are really important early on in conjunction with just close monitoring of the weight.

Dr. Brian Wood

Absolutely. Thank you for that.

patient-wishes**[21:25] Patient Wishes**

Dr. Brian Wood

So maybe then we can get into switching ART, and this will get us into some discussion about how you manage regimens and whether you ever switch regimens. But let me, as a foundation of this conversation, just share with you a situation I've seen come up in clinic a couple of times, including just recently, in terms of switching ART. So, what I have seen, for example, is a person emigrates here from sub-Saharan Africa, their HIV is controlled on efavirenz-TDF-FTC (or 3TC), you know, common combination tablets still in a lot of parts of the world. And then, a provider here switches them to bictegravir-TAF- FTC, a first-line regimen. I think it reduces a lot of efavirenz and TDF side effects, and then over a few months, they gain a significant amount of weight, a lot of weight, and then come in, and they really don't want to take this new pill anymore. This came up for me in clinic just recently. I'm wondering if you've seen similar. I'm wondering if you can talk us through factors associated with weight change and adverse metabolic outcomes after switching ART and then the considerations for or strategies for helping people in situations like that.

Dr. Sara Bares

I'm so glad you brought that up. That's not an uncommon scenario, and I think if we break it down, there are probably multiple reasons for the weight gain that occurs after that switch and the relocation. And so, we've talked a little bit about the two medications that we think may be weight suppressive and so TDF and efavirenz and so removing those two is demonstrated in, for example the ADVANCE trial, and then switching to TAF in a second-generation INSTI [integrase strand transfer inhibitor] are going to be associated with greater weight gain. Also, relocating to another country where there may be different accesses to food and physical activity and just general daily life habits are going to change too. And so, I think that becomes really challenging in terms of what do we do about it. We know both from our clinical experience and from studies now that weight gain following switch to ART is common. It's a particularly moderate weight gain on the order of a few kilos. But in practice, we see much more significant weight gain, typically is greatest in those first 24 weeks after the switch, and seems to plateau after the 48 weeks. But if it's continuing to occur even beyond that, that's when I think it is important to intervene and have a discussion with the patient about whether or not a switch may be warranted.

I think we are beginning to get some answers. Again, the data is limited, but there was the follow-up to the ADVANCE trial. Our patients who switched off from one of the assigned study regimens back on to TDF-3TC-dolutegravir lost weight and so, particularly those who switched from TAF arm to the TDF arm. And so, we have some preliminary data that switching off of TAF back on to TDF can result in weight loss. Now, what are the other sequelae? What are the risks of doing that, you know, especially in our aging population? Are we going to begin to see more of the renal and bone toxicities? The reason that we were switching to TAF in the first place, but I think it's very much a risk-benefit discussion with the patient, and assessing the whole patient, and what are the other comorbidities. Then probably most importantly, I think so often we have these intellectual discussions where I'll be in the workroom discussing the case with my fellows and we'll talk, we'll have a plan, we'll talk through exactly what we want to do, and then we'll go back into the room and present that plan to the patient and then realize that is not at all what they had in mind. They actually are really thrilled with the weight gain and want to keep taking the medication because their family is telling them they look healthy, and they're asking them what they're doing to take care of themselves. And so I think really making sure that we're asking the patient and involving the patient in the discussion from the beginning is important.

Dr. Brian Wood

Those seem like such important points to me, just to reiterate the importance of individualizing the discussion and clarifying with the individual, their goals, their impressions, and, you know, what's most important to them. That seems like such an important point to come back to.

art-switching-considerations**[25:44] ART Switching Considerations**

Dr. Brian Wood

The other thing I heard you say there is that maybe there are benefits to a switch of ART, but switching TAF to TDF, for example, while it may lead to some weight loss, might lead to other side effects and risks. And you said earlier TDF is weight suppressive, and I don't think we fully understand why or how, so there's a lot to consider there. So, as a follow-up question, I'm curious to ask you, have you made ART switches in clinic due to weight gain or cardiometabolic comorbidities? And have you seen switches be beneficial? Have you seen switches lead to either a plateauing in the weight change or weight loss?

Dr. Sara Bares

I have, I've had a few cases really similar to the one you just shared in which your patient experienced a lot of weight gain after transitioning from TDF-3TC-efavirenz to TAF and a second-generation INSTI, as well as other cases in which patients have gained weight while on their first regimen. I've switched ART in a few of these

cases. Going back to the case you just mentioned, I think the most important aspect to consider when thinking about switching ART because of weight gain is precisely what you presented as a reason for your consideration, and that's the patient's wishes. In your case, you share that the patient didn't want to take the bic[tegravir]-TAF-FTC anymore because she was experiencing too much weight gain. And I think that's key. I sometimes spend a lot of time talking through ART switches with my fellows, and then when we go back to the patient to talk through the case, we learn that they actually have no interest in switching. In one case, we did this and then learned that the patient was ecstatic to have gained weight. Her family and friends were complimenting her and telling her how healthy she looked and she felt great and did not want to switch. That said, if the patient asked to switch or if I think the weight gain my patients experiencing is leading to metabolic sequelae and my patient is open to discussing it, I do consider switching.

Before switching ART, and particularly if the patient isn't the one asking to switch ART, I like to make sure I've exhausted all other strategies and start with lifestyle interventions. Although not common, I have found that simple strategies like advising patients to stop drinking sweetened beverages can go a long way if they don't realize how many calories their consuming this way. This is particularly common in my Latino patients who drink a lot of fresh *aguas* (or juices), which are viewed as healthy because they're made with fruit and water, but they also contain a lot of sugar. If we've tried diet and exercise, I then ask whether or not my patient is a candidate for a study evaluating the benefit of ART switches in the setting of weight gain. Unfortunately, really, both the trials that were evaluating switches for weight gain are now closed to accrual. The DEFINE trial, the 24-week results were presented earlier this year, and ACTG A5391, which is exploring a switch from INSTI and TAF-based regimens to doravirine, recently closed. So those results will be very welcome when that study is complete.

In the absence of a clinical trial to help answer the question, I think about switching the patient back to the regimen they were previously on, particularly if the switch wasn't because of toxicities or virologic failure. Although we've all seen patients switch off of efavirenz-FTC-TDF who tell us they didn't realize how many side effects they were experiencing on that regimen, we've also had a number of patients tell me that they loved that regimen and miss the dreams. So, after thinking about drug-drug interactions and other things we need to think about when switching back to a former regimen, I do entertain that. If that's not an option, based on the follow-up to the ADVANCE trial, I first consider a switch from TAF to TDF, so long as the patient doesn't have preexisting renal or bone disease. That said, although the follow-up to the ADVANCE trial was certainly promising with respect to improvements in weight following a switch from TAF to TDF, this was only in female participants and the sample size was small. Lastly, I would consider a switch to a doravirine-based regimen, but this is again based on limited data. There was a cross-trial analysis that demonstrated that doravirine wasn’t associated with weight gain when compared to efavirenz or boosted darunavir. But it wasn't a switch trial, and we won't know whether or not switches to doravirine-based ART with TDF or TAF are beneficial for weight loss until we see the results of the A5391.

Dr. Brian Wood

Thanks for adding that. And really, what I'm hearing in there is that these are challenging decisions that really need to be individualized, and there are pros and cons to all of the alternative options as well. So, what you're hitting home for me is how much we need to consider this and engage our patients in the discussion. And really coming back to what you said at the beginning, help individualize the discussion about what a person is going to be able to adhere to the best and then really work with them to monitor for some of these side effects and risks. So, thank you so much, Sara, for bringing us back to that.

two-take-homes**[30:53] Two Take Homes**

Dr. Brian Wood

As a final wrap-up, maybe you could just summarize for us what you see as the biggest take-home messages here for clinicians thinking through this and helping their patients with this and with the choices of ART.

Dr. Sara Bares

Yeah, I think the biggest take homes are that there does appear to be an association between our, especially our modern ARVs and weight gain. We still don't know whether this is removal of the weight suppressive effects of some of our older generation antiretrovirals versus, a true weight gain with off-target downstream effects, or mechanisms that were not, haven't fully been elucidated yet. The other big take-home is that the current first-line regimens, although associated with weight gain, are still the best. They are really effective. They are going to be the best choice for most of our patients because they're so effective.

Dr. Brian Wood

Sara, thank you so much. Thank you for joining us today. Thank you for sharing all of your expert insights and your clinical experience. We would love to have follow-up discussions with you in the future.

Dr. Sara Bares

Thank you so much for having me.

credits**[32:00] Credits**

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