

Expert Interviews

National HIV Curriculum Podcast

Semaglutide Studies in PWH & What to Consider Before Prescribing

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Dr. Kristine Erlandson, Associate Professor at the University of Colorado School of Medicine and SLIM LIVER study senior author, discusses recent key GLP-1 receptor agonist studies, clinical implications, and practical prescribing considerations for HIV primary care providers with National HIV Curriculum Podcast Lead Editor Dr. Brian Wood.

Topics:

- CVD and HIV
- GLP1
- steatotic
- MASLD
- MASH

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Transcript

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[background](#)**[00:00] 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, individuals with HIV have higher rates of certain cardiometabolic health conditions as compared to individuals without HIV. This includes heart disease, diabetes, metabolic syndrome, as well as steatotic liver disease. All of these health conditions are closely associated. They tend to occur together, and they are and should be a major focus of HIV primary care these days. Now, there has been incredible interest in the GLP-1 receptor agonist (RA) drugs and related medications. That interest stems from a number of potential benefits related to weight loss and also improvements that have been seen in studies looking at each of those cardiometabolic health conditions.

What's new and what will be the focus of this episode is we are now seeing reports of trials and other data related to use of the GLP-1 receptor agonist drugs specifically by people with HIV. I would say that an understanding of this data and the implications, as well as practical considerations for prescribing these medications to people with HIV is important to anyone in the field of HIV primary care.

[introduction](#)**[01:27] Introduction**

Dr. Wood

Today, we are really honored to welcome Dr. Kristine Erlandson to help us review and discuss the GLP-1 receptor agonist drugs and to discuss studies of these medications and people with HIV that have come out within the last year or so.

Dr. Erlandson is Associate Professor in the Department of Medicine and the Division of Infectious Diseases at University of Colorado School of Medicine. She is an accomplished researcher who has led investigations related to HIV and aging, associations between specific ARVs [antiretrovirals] and weight change, as well as use of the GLP-1 RA drugs for people with HIV who have metabolic comorbidities in addition to having studied a number of other topics. She has received numerous accolades for her work in HIV research as well as her work as an HIV clinician and educator, and we are lucky to have her. Welcome, Kristine.

Dr. Erlandson

Thank you so much for the opportunity to join you.

Dr. Wood

I'm really looking forward to this discussion. It really has become a hot topic and very relevant to clinical

practice.

[why-do-these-studies](#)**[02:28] Why Do These Studies?**

Dr. Wood

So, let me just start by asking your perspective and opinion on why it's important to study and to better understand the effects of the GLP-1 receptor agonist and related drugs for people with HIV.

Dr. Erlandson

I think that we expect the response to GLP-1 agonists and other drugs to probably be similar in people with and without HIV in many ways. But certainly, there's some unique factors, particularly some of the side effects. We know that the GLP-1 receptor agonists are associated with a lot of GI [gastrointestinal] adverse events, nausea, vomiting, bowel obstructions, even in some cases, and knowing whether that is going to occur more commonly in people with HIV and potentially impact adherence is very important. We also know that fat is different in people with HIV, especially related to old antiretroviral therapies or even newer antiretroviral therapies. Fat may go to different places in people with HIV; it may go there more commonly, and it may behave differently. It may become fibrosed. It may be harder to get that fat to go away. So, understanding how these drugs may behave differently is, I think, of utmost importance in people with HIV.

Dr. Wood

Thanks, Kristine, for outlining that. So sounds like we, as a research committee, really need to understand will these drugs be equally effective as for people without HIV and, as you're getting at, understand any unique concerns or side effects. Would you agree with that way of saying it?

Dr. Erlandson

Yes, exactly. I think there's also a lot of unique inflammation and immune changes that we see with some of these drugs that may be particularly beneficial in people with HIV and important to understand.

Dr. Wood

I think that's a great point. We'll come back towards the end to revisit some of the specific concerns that have come out and get more of your take on any specific reservations you have for patients in your clinical practice. We'll come back to that for sure.

[slim-liver-background](#)**[04:22] SLIM LIVER Background**

Dr. Wood

Let's, as a next step, talk about a specific study that I know you were very involved in. You were senior author of the SLIM LIVER trial, also known as ACTG5371, and we recently released a [literature review episode](#) on the publication in *Annals of Internal Medicine*.

So, we've reviewed some of the details of the trial and we've reviewed some of the basic terms and definitions, but I'm lucky to be able to ask the senior author of the study your perspective on it. So you've talked a bit about why we need to research these drugs for people with HIV. How about specifically looking at those with steatotic liver disease or metabolic dysfunction-associated steatotic liver disease, which was a focus of that trial. Why did you think this study was important to conduct and if there's any background about how this trial came to be, maybe you could enlighten me and listeners.

Dr. Erlandson

Yes, there's a lot of background on this study.

Dr. Wood

I imagine.

Dr. Erlandson

We'd actually proposed it initially with liraglutide because semaglutide wasn't even available at the time that we had put together the thoughts of this study. Then semaglutide came out and was starting to look much more potent than liraglutide, so we switched gears. You'll notice within SLIM LIVER, we used the 1-milligram dose of semaglutide instead of the higher doses that are currently used. That was actually the only approved dose at the time. So important result of this SLIM LIVER study is we did see these nice changes in liver fat and weight loss even with that smaller dose of semaglutide. But the rationale behind this study was just that there's such a high rate of fatty liver in people with HIV. We oftentimes see it if we're checking an ultrasound in someone for other reasons or see that slight elevation in liver enzymes. I have so many patients I've done a liver ultrasound on and it comes back pretty fatty.

Not all people that have MASLD or metabolic dysfunction-associated steatotic liver disease, the mouthful that that word now is, not everyone progresses to the steatotic hepatitis or more advanced liver failure, but importantly, that MASLD is kind of an opportunity for prevention. So it gives us a way that we can intervene, keep people from going on to develop more liver disease. It's kind of noticing that patient that has many risk factors for cardiovascular disease, but hasn't had an event yet, and it gives us a window of opportunity to potentially prevent liver failure in a major cause of morbidity and mortality. We also know that MASLD is very commonly linked to cardiovascular disease, and I think cardiovascular disease is a hot topic right now, particularly with REPRIEVE findings coming out within the last year as well. Cardiovascular disease is probably at least two times as common in people with HIV. So if we can give a treatment that's going to help decrease some of those cardiovascular measures and cardiovascular risk factors and decrease the risk for progression to liver failure, it's just an ideal opportunity, an ideal drug, ideal patient population to really answer that question.

Dr. Wood

Absolutely. I'm really glad you added that. I was also going to raise the, what seems to be, pretty tight association between MASLD and steatotic liver disease and major adverse cardiovascular events. I think that's been seen in a number of studies now. Another thing you said there really caught my attention. This comes up a *lot* in clinical practice. In my clinic just last week, I saw multiple individuals who had a note of steatotic liver disease based on an ultrasound or a CT scan done for other reasons in individuals who have other risk factors for cardiovascular disease as well. So we'll come back to some of the implications for clinical practice. One of the things on my mind is how to prioritize people for these agents, given there have been supply shortages, there are difficulties getting them improved by insurance sometimes. So, there's so much interest, there's so much potential benefit, but how do we prioritize people, I think is a really important question and we'll come back to that.

[slim-liver-implications](#)[08:24] SLIM LIVER Implications

Dr. Wood

Staying with SLIM LIVER and the study that you helped lead, I think the findings have really important implications. We talked about some of those on the recent episode, but as senior author of the study, what do you see as the biggest take-home messages from the results and the biggest things that an HIV primary care practitioner should learn from that study?

Dr. Erlandson

I think the biggest take-home point is that these drugs do decrease liver fat. They've been looked at in fatty liver, but more commonly in NASH [nonalcoholic steatohepatitis] or more advanced disease with fibrosis in the general population, not in people with HIV. We found that in people with HIV who have fatty liver, not necessarily fibrosis or advanced liver disease, but in this specific population with just fat in their liver, we do see a very nice response with more than 30% decrease in liver fat with these drugs. It's just a reminder to primary care physicians how common this liver fat is, and when we see those subtle elevations in liver function tests, maybe do some extra imaging, see if it's there, and bring this up as a potential treatment option for patients. And then we can talk more, as you mentioned, about priorities and who do we really target for therapies, but I think some of this was just raising recognition of the condition, that it is something that's treatable.

Dr. Wood

Yeah, recognition and awareness is so important. Coming back to something that you brought up earlier, that research question, are these drugs as effective for people with HIV as for people without HIV? The findings of SLIM LIVER I think would suggest that the efficacy is high and probably similar to the efficacy for people without HIV. Would you agree?

Dr. Erlandson

Yeah, and in terms of the weight loss effect especially, we saw pretty similar weight loss effects as what's been seen in prior studies in the general population. Again, recognizing we had that lower dose of semaglutide than what's used in a lot of the obesity studies, but we certainly did see similar effects with weight loss and other improvement in triglycerides, improvement in other measures. So yep.

Dr. Wood

I see. Thank you.

[effects-on-clinical-practice](#)**[10:28] Effects on Clinical Practice**

Dr. Wood

So, kind of a big question, but how do you think those results should change clinical practice in terms of selecting individuals for these drugs or in terms of the counseling around these drugs for people with HIV?

Dr. Erlandson

We can talk more about some of the other interventions for fatty liver because still, the primary treatment for fatty liver is dietary counseling, exercise, and physical activity with the goal of weight loss. So whether that weight loss is through lifestyle interventions or through pharmacologic therapy, I think we've now shown that pharmacologic therapy is also very effective. So, still coming back to how do we treat fatty liver? I think the biggest challenge in clinical practice is trying to get these agents. And if we can have "fatty liver" as an indication that insurance would cover these agents that would be the ideal change to clinical practice is that we've demonstrated these can be effective for it. I think the potential cost benefit for patients long-term if we can reverse fatty liver, reverse the ultimate development of steatohepatitis and liver failure, that cost benefit of preventing a liver transplant could be major. But I think in clinical practice right now, it's continuing what we're doing with lifestyle management and weight loss, whether that's through lifestyle behaviors or through a pharmacologic therapy is probably the main thing that we'd like to see out of this study.

Dr. Wood

Yeah, absolutely. I can really relate to that thinking about the patients for whom I have counseled about steatotic liver disease or fatty liver. After encouraging the lifestyle changes, the dietary changes, the increase

in cardiovascular activity, there are not a lot of proven pharmacologic options. There is a relatively new agent that I have not tried to prescribe yet that I know was approved by the FDA, but I imagine would have insurance barriers. There's been a lot of controversy over the years about vitamin E and other agents, and I know aspirin may have some benefit, but there's nothing really that we routinely prescribe and feel good about in terms of efficacy and safety. So, I think what I'm hearing you say is after the lifestyle interventions, if those have not gotten a person to goal, or if a person struggling with those, this is an agent you would consider, and steatotic liver disease may be a valid indication but we don't yet know if insurance will cover it specifically for that indication. Have you tried in your practice yet to prescribe a GLP-1 receptor agonist with that specific indication?

Dr. Erlandson

No, actually, I have not. I think I've had low expectations that it would go through, so I haven't.

Dr. Wood

Same. I'll just offer the same in my practice. I don't think I have in the absence of a concomitant confirmed diabetes diagnosis, but like you, I see the benefit, and I'm eager to see that become a valid indication in the future so that we have more options.

[slim-liver-limitations](#)**[13:30] SLIM LIVER Limitations**

Dr. Wood

So, turning back to SLIM LIVER, there's so many different directions we could take this, but coming back to SLIM LIVER, I'm also curious to hear your insight. So what do you see as the biggest limitations of that study?

Dr. Erlandson

I think there were several limitations. We didn't have a control arm. Most of that was related to cost and just logistics of trying to get the study done with the expense of these therapies. Although, the amount of weight loss that we saw with the treatment is far beyond what we would expect in a population that we had provided some dietary counseling in. We basically just gave participants a handout that offered some general advice on healthy diet and activity, and we wouldn't expect that people would have a massive weight loss with that therapy. Many of the people that enrolled in this study had already had attempts at losing weight in the past and had been unsuccessful and hence some of their enthusiasm for joining this study. We don't know how long the benefits of this drug will last, and so we had a trial lasting 24 weeks. We then had follow-up over 48 weeks. Due to cost, we weren't able to repeat the MRI at 48 weeks, but we do know that people tended to regain a good portion of the weight that they'd lost over that time point.

Whether they're regaining fat at the same rate in their liver, we don't know. I think that might be an important point. Can we give people a shorter course of this, reverse some of that liver fat, and maybe the liver fat would stay away for a longer period of time if they choose not to continue on the drug due to side effects or cost or other barriers to maintaining the treatment for a longer time? Then I also mentioned that we use that lower dose of semaglutide, so we probably would've seen even greater liver fat if we had pushed that dose up to the 2.0 or 2.4-milligram dose instead of the 1-milligram dose. But in some ways, I think it's actually really nice to see this benefit that we did see with the lower dose that may be more tolerable over time, may have lower side effects over time.

Dr. Wood

Absolutely. I think that's an important lesson from the study that lower than the approved doses may be very beneficial for people, and that may help us as clinicians adjust the dose to the highest that's tolerable and the highest that's effective for someone. But you bring up an important outstanding question that the

sustainability, the longevity, the duration of the benefits really are unclear. I don't know about you, but for me, that has been a challenging part about the counseling with starting these agents is we don't really know how long it is optimal for a person to continue them or exactly what happens after stoppage.

Dr. Erlandson

I think most of the data from clinical trials, some of the trials are certainly longer. We have data for a couple of years of treatment, but obesity isn't a condition that goes away after two to three years of treatment. I mean, this is a lifelong condition. If we're keeping people on therapy for 20 years, I think the long-term consequences of that extended duration of therapy, we really don't know yet. We don't know the safety out to that length of time. So, understanding if we can maintain some of the benefit with a shorter period of dosing, I think is really important.

Dr. Wood

Absolutely. I think that's such an excellent point and that brings up some of the important future research priorities and outstanding questions.

[key-related-studies](#)**[16:46] Key Related Studies**

Dr. Wood

So, maybe I can ask you, Kristine, what other recent studies have you found to be really important in informing your decision-making and counseling of patients around the GLP-1 receptor drugs?

Dr. Erlandson

I think within the HIV field there's a couple of studies. Dr. McComsey presented some data at ID Week in the fall of last year [[The Lancet article](#) published after interview was recorded] and then they had some [updates at CROI](#) [Conference on Retroviruses and Opportunistic Infections] this spring that showed a similar benefit with semaglutide in patients that had lipodystrophy with HIV, and they had a nice loss of weight in their population. There's another study that's still enrolling in Dublin, looking at semaglutide for weight loss as well. I haven't seen any results from their studies yet, but I think those two studies will help us gain more appreciation of the safety and efficacy of these agents in people with HIV. In the general population, I think it's just been really interesting to see the benefit on other disease processes like diabetic nephropathy, and congestive heart failure, and other endpoints, and just the potential benefits well beyond weight loss.

I've seen some emerging trials. I'm not sure how many of them have been published yet in the larger form. Many just small pilot studies looking at these drugs for addiction from other substances and so can we decrease smoking, decrease other substance use, and then potential cognitive benefits. I think there's a couple trials underway with Parkinson's, or Alzheimer's, or other conditions. So, I think there's a lot to learn about these agents well beyond the impact on obesity and weight-related conditions. So, really exciting.

Dr. Wood

It's really fascinating. I've seen some of that literature as well. I can't say I fully understand the mechanisms behind some of those potential benefits, but it seems like there are a wide array of conditions that may improve with these agents.

[lipoatrophy-muscle-loss](#)**[18:39] Lipoatrophy and Muscle Loss**

Dr. Wood

Maybe I can come back to concerns a bit because you mentioned the abstract presented by Grace McComsey

and colleagues, which showed a lot of potential value in agents but also raised a bit of concern, especially for people with a history of lipoatrophy and raised some concern around the potential loss of subcutaneous fat. I wonder if that comes up for you in clinical practice and how you integrate that into your counseling.

Dr. Erlandson

I haven't had enough patients able to take them to get enough weight loss from these agents that people have complained too much of the loss of facial fat, but that has certainly been a lot of awareness on the news. I think that so-called "Ozempic face" that some patients have raised concern. I think that could be even more important in people with HIV who do have underlying lipoatrophy and whether that could worsen some of their lipoatrophy. We've been particularly interested in the potential impact on loss of muscle as well. We know that anytime someone loses weight, they also tend to lose skeletal muscle as part of the weight that they lose, and the more rapid that weight loss, probably the greater the amount of skeletal muscle loss, especially if someone's not doing resistance exercise to try to maintain that. I think Dr. McComsey had found similar results in her study. They looked at DEXA scans from their study population and found that there was a loss in DEXA-measured lean mass in her study in the treatment group, and then I think a slight gain, maybe, in their control group.

We looked at a different measure of muscle, just based on the muscles in the trunk that were surrounding the liver that we were able to capture on the MRI, and similarly saw a decrease in skeletal muscle area from those MRI-measured muscle outcomes. Importantly, we also included a measure of physical function, looking at how quickly someone can rise up from a chair or how quickly someone can walk a short distance on a four-meter walk. We presented [that data at CROI](#) this past spring and saw a trend towards improvement in physical function. It wasn't statistically significant, but at least we saw that people weren't rapidly declining or having major declines in their physical function. We think maybe just some of the decreased weight that people are carrying allows them to get up from a chair faster and move across the room faster. Some studies have shown improvement in subjective reports of physical function, so people feel like they're doing better. We didn't really see major changes in physical activity, so that was outside of changes that people were having to their general physical activity.

So, I think that although there may be this loss in lean mass, it may not have clinical implications, at least in this short period of time. More importantly is when we're prescribing these therapies to older adults who already have had quite a bit of loss of muscle, especially older adults with HIV, is trying to incorporate resistance exercise or some of the things that we don't tend to necessarily prescribe very well as prescribers. Telling patients to go to the gym and lift weights a couple of times a week may be more important than we realize.

Dr. Wood

Absolutely. I think that's such a great point, and I'm really glad you and your group are looking at changes to muscle mass and physical function and changes over time. So, thank you for adding that. We included a link to that CROI abstract in our last episode transcript as well, so listeners can take a look at that, as well as the abstract from Dr. McComsey and colleagues.

[patient-counseling](#)**[22:13] Patient Counseling**

Dr. Wood

So, Kristine, you've outlined a number of potential benefits, and then there, I heard a couple of concerns and a couple of clinical features that might give you pause in terms of considering these agents. So, let's just come back to the day-to-day clinical practice. Maybe to start with, how does your counseling to patients go about pros and cons of these drugs and potential duration of use?

Dr. Erlandson

I think that the pros are oftentimes that many patients have struggled with trying to lose weight in the past. They've attempted dietary changes, they've attempted physical activity and just have not been able to successfully lose weight. This really offers an effective option to help lose weight and to help take away some of those metabolic risk factors for cardiovascular disease, for liver disease, for many of the comorbidities we've just discussed. However, most of my research outside of this specific study is really focused on lifestyle modifications, dietary changes, increasing physical activity, in part because there's so many other benefits of those interventions on health beyond just that focus on weight and on metabolic outcomes. I think physical activity has benefits on cognition, on physical function, on cardiovascular health, cancer, the numerous different things that we know exercise can help with, and GLP agonists can certainly improve some of those outcomes, as we talked about. But I think we don't necessarily know some of the long-term consequences of GLP therapies. We also know that as people take GLP agonists, they tend to decrease their food intake.

So, enhancing what people are actually eating and making sure it's the highest quality food is incredibly important. Just because you consume less food doesn't necessarily mean what you're consuming is getting those important nutrients and minerals and vitamins that you need for brain health, and for muscle health, and all of those factors. So, I think making sure that we're still adequately counseling people in the importance of nutrition and physical activity, even if it's not for the purposes of weight loss, but it's for the purposes of maintaining brain health and muscle health and skeletal health and all those factors over time is really important. Then, I think just the cons, as we talked about, it's primarily drug availability and that cycling on and off of therapy. Do we know that we can give this drug long-term? I've had patients in clinic that have diabetes that haven't been able to fill their prescription regularly, and then they're on and off of therapies and constantly trying to find a new pharmacy that can fill the agent because one pharmacy's out.

I don't know that those long-term yo-yo effects of weight gain and weight loss are going to have a beneficial effect. So kind of understanding what those consequences of going on and off these medications might be. Then, as I mentioned earlier, I think the very long-term side effects aren't well known, and neither are some of the long-term effects in older adults, who may be more prone to some of the GI effects or dehydration or muscle loss.

[prioritizing-patients](#)**[25:16] Prioritizing Patients**

Dr. Wood

So, that leads me back to the question about who, as clinicians, we might prioritize in our clinical practice, especially our HIV clinical practice for these agents? I wonder for you in your practice what you think or who you might be prioritizing right now?

Dr. Erlandson

I think insurance-wise, I tend to prioritize those that have diabetes because those tend to be the patients that we can get these therapies for, and I think that they have many different benefits from these agents. So, I first prioritize those with diabetes. I think obesity with complications, and so if someone has cardiovascular disease, if they have MASLD, if they have other complications, sleep apnea, or other complications related to their obesity, those are my first priority patients to try to get access for these therapies. Other agents might be good for some other patients first. Oftentimes, I think insurance is going to require us to have tried several therapies that have failed before they'll cover these therapies. So, trying to introduce some of those other therapies upfront might be good for other patients.

[26:23] Other Therapy Options

Dr. Wood

I think that makes a lot of sense. Do you have insights into other therapies you tend to try first either for steatotic liver disease or for helping people with weight loss?

Dr. Erlandson

I think any of the approved therapies have potential side effects, potential costs, potential insurance therapies. Most of it's a discussion with the patient as to "What's triggering to you? Are you having food cravings?" in which maybe one of the therapies that has the suppressive effect on food cravings might help. Are there concomitant mood disorders that one of the therapies that introduces a little bit more antidepressant effect might help? Are there comorbidities in which we maybe don't feel comfortable using phentermine or something that might contribute to tachycardia or some sort of other cardiovascular issue. So, mostly, it's a patient-by-patient, looking at their comorbidities and what medications might be approved.

Dr. Wood

I think that's great. That seems like such a great strategy to me, and it's something I will take back to my clinical practice as well.

[future-research-priorities](#)**[27:23] Future Research Priorities**

And so, maybe before we wrap up today, you could outline for us what you see as the biggest research priorities for the future around the GLP-1 receptor agonist drugs and related meds? Where would you like to see the research field go?

Dr. Erlandson

I think as these drugs are getting prescribed for longer periods of time, understanding the long-term safety is going to be incredibly important. I'm going back to some of the trials that have already been completed and looking at who stayed on the therapies and the phase 4 studies where we're looking at real-life practice and who develops complications long-term. As I mentioned, I'm particularly interested in physical function, and so I think understanding the consequences of these therapies, when prescribed to older adults, in the loss of muscle over time is going to be important. Then I'll just say that ultimately, I think these drugs have really changed our approach to obesity, and I have many more patients coming into clinic and willing to talk about their weight. So just kind of what are the secondary effects of these drugs on our recognition and kind of acceptance of obesity and ability to talk about it with patients, because I think sometimes it was a taboo subject for years. It's really opened up the door to having those conversations with patients.

Dr. Wood

You know, I think that's such a good point, and I don't think I've heard it stated quite like that before, and I think that's really true. Talking about it in clinic and integrating it into an overall focus on health and learning how to talk about it in a way that really promotes body positivity and recognizes body diversity and isn't shaming to people, I think, is so important. So I'm really glad you brought us back to the importance of having open conversations about this, conversations that are not shaming or stigmatizing, and that integrate an ongoing focus on nutrition, on physical function, on strength training, and exercise. That just seems like such a fantastic whole body, whole person approach. So, I really want to say I appreciate the way you presented and described that.

[take-home-message](#)**[29:23] Take-Home Message**

Dr. Wood

So before we wrap up, Kristine, any final take-home messages, final things you'd like to share with listeners before we end the episode?

Dr. Erlandson

I think just emphasizing that these are one tool in our toolbox of improving health of people with HIV that aren't probably the answer to everything and that there's still many interventions that we can continue to supplement these therapies with, but they're certainly an exciting new realm of considering weight and weight-related complications. Then just a huge thank you for the opportunity to come and talk with your listeners today.

Dr. Wood

Thank you so much for your time and for this excellent discussion. I appreciate it very much.

[credits](#)**[30:08] Credits**

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[before-prescribing](#)