National HIV Curriculum

Literature Reviews

National HIV Curriculum Podcast

The SLIM LIVER Study: Use of Semaglutide for Persons with HIV

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Season 1, Episode 12

This episode reviews literature about the recent SLIM LIVER study which evaluated the impact of semaglutide, a GLP-1 receptor agonist, on persons with HIV and discusses the important implications on clinical practice.

Topics:

- CVD and HIV
- diabetes
- MASLD
- obesity
- IHTG

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Disclosures
Disclosures for Brian R. Wood, MD

References

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In this episode:

[introduction](#)**[00:00] Introduction**

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

In today's episode, I am going to review a recent publication on the use of a GLP-1 receptor agonist drug called semaglutide for people with HIV (PWH) who have clinical evidence of MASLD, a term that stands for metabolic dysfunction-associated steatotic liver disease which we will talk about. This is one of the first publications of a clinical trial of a GLP-1 receptor agonist for people with HIV. I think the findings have important implications for clinical practice, and I'm excited to review this for you.

The full title of the publication is "The effect of open-label semaglutide on metabolic dysfunction-associated steatotic liver disease in people with HIV." The paper was published by Dr. Jordan Lake and colleagues as a [brief research report](#) in the Annals of Internal Medicine. It first came out online in April 2024 and in print in June 2024. With permission from the journal, we are going to include copies of the tables as part of the podcast transcript, so if you are in a place where you can look at the podcast transcript or look at the actual paper while you listen, you will be able to see the full tables of results If not, I will summarize the results for you.

[glp-1-basics](#)**[1:40] GLP-1 Basics**

Now, this is the first literature review in our National HIV Curriculum Podcast and before we dive into details of the study, I'd like to offer some background and definitions.

First, I'm sure many listeners are familiar with the GLP-1 family of medications, but let's review some basics so that we're all on the same page. The GLP-1 receptor agonist (or GLP-1 RA) drugs, also called GLP-1 analogs, have been in the press a lot lately. These drugs are synthetic compounds that mimic a natural hormone called GLP-1 (or glucagon-like peptide 1). That hormone is released by our intestines after eating after we eat and that hormone has a number of effects. It stimulates pancreatic beta cells to release insulin, while also suppresses the release of glucagon from pancreatic alpha cells; the net effect is the lowering of blood sugars, but there are a number of other effects as well. The GLP-1 hormone decreases pancreatic beta cell apoptosis, delays gastric emptying, decreases glucose production by the liver, increases glucose uptake by muscles, and also reduces feelings of hunger through actions by the hypothalamus. There is a related drug that combines a GLP-1 receptor agonist with a GIP analog; GIP stands for glucose-dependent insulinotropic polypeptide. GIP is a hormone that has similar effects as GLP-1.

So, all of the drugs in this family have been found to have potential benefits for people who use them regularly. They've been found in studies to induce weight loss, improved A1C, improve blood pressure and cholesterol levels, as well as improve cardiac function and reduce risk of major cardiac adverse effects. There's also been data showing prevention of progression of diabetic nephropathy, and there's been a lot written in the literature and the press about potential other benefits as well. There are certainly downsides to these drugs. There's absolutely concerns, potential adverse effects, and, I would say, a lot of unanswered questions, and I will come back to some of these issues and concerns later, but clearly many people can benefit from these meds. Certainly, many people are interested in the meds. I get a lot of questions about them in my clinical practice. There have been supply shortages around the world. They've been in the news a lot, so I do think it's worthwhile to have an awareness of these medications. I think a lot of the unanswered questions people are exploring through research and people are figuring out to optimize them in their clinical practice and specifically I think it's important that we build data on efficacy and safety for our patients who have HIV.

Now, I won't go into a lot of detail about the specific GLP-1 receptor agonist drugs or the related meds. I think it's important to know that there are subcutaneous and oral options, as well as weekly or daily dosing options, all approved by the FDA. I'm sure you have experience in your clinic medical practice helping people choose

which is right for them and helping get insurance approval. I'm sure many of you know how challenging that can be. But, again, I think it's important to build our understanding of these medications, including both the efficacy and the safety.

study-terminology[5:32] Study Terminology

Let me next just give three definitions that I think will help when interpreting the specific study I'm reviewing today.

- First, MASLD, as I mentioned, is an important term defined as steatosis of the liver plus metabolic syndrome. It's the new nomenclature for what was previously called non-alcoholic fatty liver disease. I just want to say I agree with the new naming. I think it's less stigmatizing. I think it's also a more accurate description of the overall disease process and some of the corollary risks.
- In the paper, if you review it, you'll see the abbreviation SLD, which stands for steatotic liver disease. That's an overarching term for a buildup of excess fat content in the liver, which can be caused by either metabolic dysfunction, alcohol use or both.
- And the authors of this publication also use the abbreviation IHTG. I'll admit I wasn't very familiar with that before reading this study but that stands for intra-hepatic triglyceride content. It's a way to measure the fat content in the liver. To measure it, the investigators used a specialized MRI protocol termed MRI-PDFF for magnetic resonance imaging proton density fat fraction. I won't go into details about that type of MRI. Honestly, I couldn't even if I tried, but I just want you to be familiar with some of the terminology, and I will be using some of these abbreviations.

study-rationale[07:12] Study Rationale

Now, let's review some of the details of this specific study. This trial was called ACTG5391 or the SLIM LIVER trial. It focused on the effects of semaglutide, or semaglutide if you prefer, primarily on liver health but also on other outcomes for people with HIV. The authors provide the following basis for the study: First, MASLD is a growing epidemic and is highly prevalent in individuals with HIV. Second, steatotic liver disease is an independent risk factor for cardiovascular adverse events and people with HIV have overall higher cardiovascular disease risk than people without HIV, so addressing steatotic liver disease both for liver health and as a risk factors for major cardiovascular adverse events is really critical for care for people with HIV.

Now, semaglutide is a GLP-1 receptor agonist drug approved by the US FDA [Food and Drug Administration] for diabetes, also for weight loss, also now for cardiovascular disease prevention in people with cardiovascular disease and obesity. It's been shown to improve cardiovascular disease risk and steatotic liver disease for people without HIV who have diabetes, and there's definitely a lot of interest and relevance to the field of HIV medicine.

study-design[08:50] Study Design

Thinking of the objectives of this specific trial, the authors describe it as a pilot study with the goal of assessing the effects of semaglutide on intrahepatic triglyceride level in people with HIV with clinical evidence of MASLD. Their hypothesis was that semaglutide would reduce IHTG and improve cardiometabolic parameters.

- Their study design was a phase 2b, single-group, open-label trial of semaglutide for people with HIV who had documented central adiposity, insulin resistance, or prediabetes, plus evidence of steatotic liver disease not caused by alcohol use. I'll give some more detail about the inclusion criteria and how they defined some of those things shortly.
- The primary endpoint of the trial was 24-week change in IHTG as quantified by that MRI protocol I mentioned.
- The study enrolled in the U.S. and Brazil. Eligible participants were age 18 or older. All had suppressed HIV RNA levels on ART [antiretroviral therapy]. And all had evidence of liver steatosis; their criteria for

that was at least 5% IHTG by a baseline MRI. Participants reported no significant alcohol consumption, and as I mentioned, all had evidence of metabolic syndrome in addition to evidence of liver steatosis. Specifically, all had elevated waist circumference and laboratory evidence of insulin resistance or prediabetes.

- Based on power calculations, investigators calculated a need for 50 participants in order to achieve at least 90% power to detect an absolute change of IHTG of 5% or more. When we get into results, I'll note the results primarily come from a per-protocol analysis, meaning they included participants who received semaglutide within 4 weeks of their week-24 MRI.
- The study intervention, again with semaglutide, but I want to note the way they did this. It was self-administration each week by subcutaneous injection, titrating up to a dose of 1 mg each week. I note the dose because 1 mg weekly is the dose approved by the FDA for diabetes, and it's lower than the dose approved and sometimes recommended or used for weight loss, which is 2.4 mg weekly. My understanding is that during development of the protocol for this trial, that weight-loss dose had not yet been approved and that's what led to the choice of 1 mg weekly. Participants in the trial administered the semaglutide for up to 24 weeks.

baseline-characteristics[12:06] Baseline Characteristics

Turning to findings and results. If you are reviewing the publication, I'll just summarize what I think is important:

- There were 51 enrolled participants overall, 49 included in the per-protocol analysis. The median age was 52, over half were men and just over one-third were women.
- Participants were racially and ethnically diverse.
- The median BMI at baseline was 35, which qualifies as class 3 obesity; the median waist circumference was elevated at baseline.
- And, as I mentioned, all participants had well-controlled HIV. The median CD4 count was about 700 and 100% had baseline HIV RNA levels below 50 copies. At enrollment, most participants were taking an integrase inhibitor-anchored regimen, a smaller number were taking an NNRTI as the anchor, and very few taking a protease inhibitor.

study-outcomes[13:25] Study Outcomes

If you have the paper in front of you, Table 2 shows the changes in various outcomes. Again, this is comparing baseline to 24 weeks by the per-protocol analysis as I described. Now, the primary result is significant. Investigators did observe a significant reduction in intrahepatic triglyceride content over the 24 weeks of semaglutide use. There are a couple of other really important findings that are emphasized in the paper:

- Twenty-nine percent of participants actually experienced complete resolution of MASLD. I think that's a very impressive finding.
- Plus, 58% had a relative reduction in the IHTG content of at least 30%, so a very dramatic reduction in IHTG level. And the investigators emphasized that a reduction of 30% is important because that's the threshold when histological improvement is generally seen on a liver biopsy.

So, overall, there were significant improvements in intrahepatic triglyceride content, in steatotic liver disease, and in clinical criteria for MASLD.

Now, some corollary finds: Did weight decrease? Yes. For most participants, weight did decrease, consistent with other studies of GLP1-receptor agonists in people with or without HIV. The mean weight, mean BMI, and mean waist circumference did decrease for most participants. The mean weight loss was around 17 lbs. at 24 weeks. Participants also experienced improvements in other markers of cardiometabolic health. There were improvements in fasting glucose, A1C, lipids, as well as ALT levels. There also were improvements in anthropometric measurements, glucose regulation markers, triglyceride concentrations, and other

cardiometabolic health measurements.

Now, I've heard the investigators of this trial comment in other forums and other settings in this specific publication that weight loss and improvements in liver fat content were tightly correlated. Participants who responded to semaglutide and experienced weight loss were the participants who were most likely to experience improvements in liver fat content and the other markers of cardiometabolic health. A small proportion of participants did not respond to semaglutide, and that's been found in persons without HIV as well.

Overall, the drug was very well tolerated. Most adverse events were grade 1 GI [gastrointestinal] symptoms, which is what we would expect in people without HIV. There were no specific tolerability or toxicity concerns related to the HIV itself or the ART.

study-discussion[16:30] Study Discussion

So, turning to the discussion and some conclusions. Overall, this pilot study demonstrated that semaglutide is highly effective as therapy for MASLD for people with HIV. The drug induced clinically significant improvements in intrahepatic triglyceride content and in traditional cardiovascular disease risk factors. So I think an important conclusion can be made that semaglutide has the potential to reduce cardiovascular disease risk for people with HIV and also to prevent progression of liver disease. Again, there were no specific HIV-related safety concerns and that's important.

In the discussion portion of the paper, the investigators note that the findings are similar to a different study of people without HIV that used a higher dose of semaglutide (approximately 2.8 mg weekly for 72 weeks), so they note that a implication of the current study is individuals do not need so high a dose and do not need such a long duration in order to see the benefits to steatosis in the liver or to cardiovascular disease risk. Now, the authors of the study do acknowledge several limitations, including a small sample size and the absence of a control group.

take-home-questions[17:57] Take-Home and Questions

So, what are the biggest take-home messages from this trial and what are the outstanding questions? I think a take-home message is that semaglutide and related drugs certainly can benefit people with HIV. The benefits can be expanded to include steatotic liver disease and to include MASLD; clearly, this drug led to very significant improvements in these parameters. I think the outstanding question is, given the insurance barriers, given drug shortages, given challenges of getting these meds to people who need them, how should we prioritize them in our clinical practice? And I think that that is an outstanding question that is absolutely open to debate. But, overall, I think it's important to know from this trial that patients lost weight. They experienced benefit to liver health and cardiovascular health even with lower than approved standard weight-loss doses.

So, what this reinforces to me is that for patients for whom we do prescribe these meds, we can start at low doses, titrate up slowly, and help them to find the right dose which balances benefits along with tolerability and minimizing side effects. For many that optimal dose is going to be lower than the highest possible or even recommended dose.

There are certainly a lot of remaining questions about these drugs, both for people with HIV and without HIV. Questions like, if a patient experiences a plateau in the benefits after starting the drug, how can we help to optimize that? How long should the drugs be continued and what happens after they stop? How much of the benefits revert? And also, what is the best way to address side effects, improve tolerability, and help people be successful with these meds? I would say that most of these questions and concerns are generalizable and relevant to people with HIV and without HIV.

In terms of concerns specific to people with HIV, I encourage you to look at an important study that was

presented during the ID Week 2023 Conference by Dr. Grace McComsey and colleagues. The presentation was titled "Effects of Semaglutide on Adipose Tissue in HIV-Associated Lipohypertrophy." A link is available in this episode's transcript. Alot of benefits were found and one specific concern that came up was potential loss of subcutaneous adipose tissue and the potential impact on individuals who are already struggling with lipoatrophy. So that's one concern that might be more specific to people who have HIV.

Another general concern about these agents is that while they lead to loss of fat and the benefits we talked about, they may also lead to loss of muscle and decreases in physical function. I won't go into a lot of detail; I will just comment that there was an abstract presented at CROI [Conference on Retroviruses and Opportunistic Infections] that I thought was very important. This abstract was titled "Effects of semaglutide on muscle structure and function in the SLIM LIVER study" and the abstract was presented by Grace Ditzenberger. A link is available in this episode's transcript. It also was an analysis of participants in the SLIM LIVER trial and in that sub analysis, investigators looked at changes to muscle content, muscle volume, and also physical function, and I would encourage you to look at that one as well. Overall, I would say the findings were reassuring, but I do think we need more studies. We need a better understanding of the risks over time and also how best to prevent muscle and physical function loss in patients for whom we're prescribing these drugs. I know there are ongoing studies that look at use of the GLP-1 RA drugs combined with physical exercise. I'm eager to see that data.

When I counsel my patients who are starting these meds, I always include encouragement for ongoing healthy eating, engagement with a nutritionist, ongoing cardiovascular exercise, and strength training exercise, and I talk about the potential for loss of muscle mass. So, I think that's something we need to better understand and keep in mind when we are discussing these meds or patients.

I will just end by noting that I'm also looking forward to future conversations about these medications here on the National HIV Curriculum Podcast. I'm planning a conversation with an expert in the field to get more into details of the research around use of these meds for people with HIV and also talk more about clinical practice and experience. So stay tuned for future episodes that will explore the pros and cons of these meds for people with HIV in more detail.

But for now, thank you very much for listening to the National HIV Curriculum Podcast and stay tuned for future episodes.

credits**[23:18] Credits**

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