Clinical Education Initiative
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ECHO: PREP, NEW OPTIONS, NEW GUIDELINES

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All right, so today, happy to be here with you today. And we're gonna be talking about what's new in the world of PrEP. We're going to learn about long acting, injectable PrEP and where it fits into our current HIV prevention strategies. We're going to talk about understanding the benefits and limitations of each of our available PrEP regimens. And we're going to review updates to the treatment guidelines. But before we start, there are new clinic cards available with the new guidelines. So quick cards to have in your pocket to remember the guidelines. And don't forget that there's a podcast as well for CEI. And if you have any questions, all right, so let's get started. First, a brief history of PrEP. So PrEP is now 10 years old, it is a decade old, it was in 2012, that the FDA approved daily TDF FTC for PrEP. And several years later, seven years later, it approved TAF FTC as well, for MSM and transgender women for sexual exposures. In 2020, there was a major update to the guidelines for New York State not for the CDC, where New York state supported the use of on demand PrEP, as well as other things which we'll talk about the CDC did, now does now support on demand PrEP, with their most recent update. And in 2020, we got a TDF FTC generic. It wasn't until mid to late 2021, though, that the prices really dropped on that generic giving us a really affordable PREP option. And then just a few months ago, at the very end of 2021, we got our first long acting injectable PrEP. So what's new in the PrEP guidelines, as I said New York State, CDC updated end of 2021 New York State updated may 2022. We're going to talk about the new there's many things in the guidelines, I'm going to focus on three areas. One is the new drug cabotegravir, LA or apretude I'm going to talk about guidance on choosing a PrEP regimen and then the new testing and monitoring algorithms. And just as a side note, I'm not going to be talking about today, but the CDC did add TAF FTC, as an option added on demand dosing and added same day PrEP initiation to their guidelines at the end of 2021, all of which were in New York State's guidelines by 2020. All right, so let's start with the new drug. So the new drug is cabotegravir la brand name is apretude. What is it? It is a long acting integrase inhibitor it is given as a single intramuscular dose, monthly time once a month for two months, and then every two months, plus or minus one week. I'm going to talk Okay, let's just so first I wanted to give you some of the data for the approval of of long acting cabotegravir la. This is a busy slide, but I'm going to walk you through it. There are two main studies for cabotegravir la one is O eight three, and the others O eight four the only difference between the studies is who were the participants and where it was. where it took place O eight three is MSM and transgender women. That took case that took place in a number of countries, including the US and notably in the US. It had the study population had to include at least 50% under the age of 30, at least 10% transgender women and at least 50% African Americans so really trying to get affected communities and it actually met all those goals in the in the enrollment, which is fantastic. O eight four was at sexually active cisgender women in Sub Saharan Africa. The protocol was such that everybody got an oral lead in of either cabotegravir ear, orally or TDF FTC placebo or the reverse. And why the lead in was a because we're getting ready to give somebody an injection of medication that is going to sit in their body for several months at a time. And if there's an adverse reaction is a pretty new drug, if there was an adverse reaction, the question was like, you can't take it back

out again. So everybody got an oral lead in oral medications for the first month and then either got cabotegravir la every two months or a sham injection, everybody got injected, got an injection, either medication or placebo, and pills also medication or placebo. And that was projected to go out for three years and then switch over to TDF FTC for the next year. But both of these studies were stopped early because the results were so market and it was felt like it was no longer appropriate to continue with this study. And we'll look at what those results are now

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getting My computer to wake up. Alright, here we go. So this is the O eight three study and what you can see is 13 infections in the cabotegravir arm as opposed to 39 infections in the tenofovir arm TDF FTC, it's actually only 12 infections in the cab arm one infection was found to be one person was found to be infected at baseline. So 12 new incident infections versus 39. That result is large enough to be considered statistic for cabotegravir to be considered statistically superior. O eight four looked very, very similar, with only four infections in the cabotegravir arm and 36 in the TDF FTC arm also statistically superior, so statistically superior, does that mean it's a better drug? Well, if taken as directed, both drugs are really, really strong and effective. The difference here is about adherence. And that's the challenge of oral medications, right? So if all of the infections in the tenofovir arm were really for people who are not adhering to the regimen as well. And so when you, four folks who are having challenges with adherence, cabotegravir is a really good option. But I don't think we want to call it a better drug, we just want to call it better in certain circumstances. So with after the studies came the question of whether to continue lead in or to not lead in, and in fact, there were no hypersensitivity reactions seen during either oral lead in, or during cabotegravir treatment, or prevention studies. So oral lead in is now optional. What are the benefits of oral lead in? Well, you know, it gives some, we can be absolutely sure that somebody's not going to have a bad reaction to this drug. But what are the risks of oral lead in, you're putting somebody on oral medication. And if they want an injection, because they're having any kind of challenges around adherence, you're giving them another month of potential risk. So I think we have to individualize and weigh the risks versus the benefits of an oral lead in. So this is an exciting new medication, I think, community members are super excited about it. It's been, it's one of the holy grails of treatment to have long acting medications, so people don't have to take a daily pill. So the benefits of cabotegravir la, an exciting new option, which is indicated for all sexual exposures, not for blood exposures, but all sexual exposures. It's every two months since the injection instead of a daily pill is essentially it is directly observed therapy, we know that whether somebody's getting the medication or not. And it really increases access to PrEP for a number of people who either can't or won't take a daily oral pill, have challenges with swallowing pills have privacy or disclosure concerns about having pills at home. And, or have adherence challenges due to a myriad of issues that people have. That causes challenges with adherence, or somebody who is intolerant of our current options and needs a new option. So really having new options is a really, really good thing. Actually, I have to fix this, I'm sorry, this, I think came from my cabotegravir for treatment slide. So it's a deep injection times one knot times two, if you're given cabotegravir for treatments, capital, pepper, and it's two injections, so I apologize for that. But it's a deep intramuscular injection, it's not a lot of times people say oh, I'd like that injectable because they're imagining like getting a vaccine or getting a diabetic injection or getting

something that they're used to. This is a deep intramuscular, intra gluteal injection. So not something that can be done at home, and something that people are going to definitely feel there are injection site reactions, which we'll talk about. It does require at least six in person visits per year. So now we're at a point where somebody who's stable on oral PrEP can maybe come in once or tw ice a year, but get their labs quarterly, they don't have to have such such frequent visits. But for this, they're coming in all the time. And for some people that's a barrier having to come in all the time wait, get the injection Wait. There's also the potential for breakthrough infections despite on time injection. So in the study, even though people weren't 100%, adherent, we know, because they got their injections. There were some breakthrough seven to date.

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There is a delayed antigen antibody conversion, which we'll talk about at some length. There's also the potential for integration resistance if you acquire HIV while you're on this, and there were five cases of integration resistance that developed and the people who developed HIV while on this medication. There's a long tail phase once this treatment is discontinued, I'll talk about that cabotegravir doesn't treat Hepatitis B so for Hepatitis B patients tenofovir is a better option if they need treatment. Although if they don't tolerate tenofovir they can get cabotegravir for PrEP and use another alternative Hepatitis B treatment. It's not appropriate for people who have injectable fillers or silicone in the gluteal areas, because we can assure absorption and that the Depo medication will sit in the area in the right way. If there's silicone or filler in the area, we can't same day start, the authorization process is way too cumbersome, way too difficult. We're not gonna be able to get people same day medication. The cost compared to other at least one other option, which we'll talk about. And then there's all the logistics of implementing this. I don't know if anybody who's in this, and we can talk about that after my presentation who's on in this webinar has instituted it or is trying to institute it in their facility, but it is really, really challenging. So first, the injection site reactions. So this is a graph showing the O eight three study. And as you can see, if you look at the left hand side, injection site reactions were very, very common initially, and a majority of those in the first injection were considered moderate. But mild to moderate and a few severe grade three in reactions. Some people had no reaction even from the start. But as you can see, the reaction diminishes over time and becomes majority grade one with some more moderate grade two reactions. For most people, this injection site reaction starts about a day after the injection and lasts a day or two. So another issue with this. One issue with this medication is that there is a long tail a long pharmacokinetic tail. It takes a very long time for this medication to clear from the body from the studies. In the studies cabotegravir Was it was detectable for over a year, some level of cabotegravir was detectable for over a year after the last injection, and meeting a 43.7 weeks for males and 67.3 weeks for females. So what does that mean? If somebody decides to stop taking medication or disappears from our care and isn't on an oral medication and gets exposed to HIV, while the levels are dropping, you can get to a point where the levels aren't strong enough to actually prevent HIV, but there's enough drug in the system to cause a selective pressure for potential integration resistance. So the official recommendation is if somebody is going to stop cabotegravir and continue to be at risk, they should be covered for with tenofovir base PrEP for at least a year to cover that tail. The good news is that in the O eight three study, we don't have data yet for O eight four. But in the O eight three study, there were no resistance

mutation seen for people who got HIV to develop HIV acquired HIV while they were in the tail phase. So we haven't seen that happen yet where they got resistant, a integration resistant HIV, but it is a potential concern. All right, another really busy slide, but I want to walk you through it very, very quickly. These are the 12 new incident infections and for baseline infections in the cabotegravir la arm of O eight three. So Group A, those are people who got a baseline infection. Group B, there were five those are for people who actually after the fact were found to have HIV but then they started on the oral lead in. There were B there were five infections after a prolonged delay in dosing. So people who got in it got either oral medication or got injections. But then there was a big delay in getting another dose for people sort of dropped off of medication. C three infections during oral lead in. Again, the concern about oral lead in in people if there's adherence challenges getting HIV during that oral lead in phase. And there were four in this study that were for infections, despite on time cab dosing, as I've said there, several others that have developed since this study was first reported there's no seven infections overall, despite on time cabotegravir dosing

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in terms of when somebody's got HIV versus when their HIV was actually detected is a very big issue. And I'm spending time on this because it really points to what the guidelines are saying around testing. And so in. So let's take one of these. Let's look at let's see, let's look at D the first one D one 100%, the little green squiggly thing towards the end is where the person actually in retrospect, when they went back and looked at prior samples, there was actually HIV virus detected then but the HIV antigen antibody tests that the fourth generation and But he tested and didn't detect it until much later. And that's a scenario we see actually with this over and over again, if you look at particularly all the Ds, you can see that in going backwards after somebody's HIV test seroconverted, when they went backwards to see when the first virus was there looking at viral load, they found the virus to be there much earlier than the HIV test told them. And so in Cabotegravir, there was a delay of 62 days for baseline infection. So if somebody was, was positive at baseline, it took 62 days for an HIV test to tell us that that person was positive because the medication once the effect and delays the zero conversion, for new infections for incident infections, infections, it was even longer 98 days from the time of infection till the time that the HIV test turned positive. We see the same effect with any medication, we see it with PEP and we see it with PrEP. But but the the time delay is much shorter. For TDF. And FTC, the delay from baseline to detection was 34 days and incidents infections, 31 days from the time somebody could actually first find virus in retrospect to when their HIV tests actually turned positive. So there's a delay but not as long, and that will come back into play. So that delayed detection of new HIV infection, as I said, 98 days for cabotegravir thirty one for TDF FTC, that delay detection, lead to integration resistance, and the loss of a whole class of HIV treatment for several patients, as I said, Five in this study. So some of the question is, if we can find it earlier, can we prevent integration resistance, even if somebody's seroconverts well, on cabotegravir for TAF, or TDF FTC, the story's a little bit different. Resistance upon failure is really infrequent. It almost always happens if somebody has undiagnosed HIV at the time of initiating PrEP. But again, it's possible after but that's oftentimes when we'll see it. If somebody does fail PrEP TDF, or TAF, PrEP with resistance, which is not uncommon, it's almost always the 184 VRI mutation, that mutation doesn't impact potential HIV treatment, including our first line treatment, so you're not losing treatment options like you are

with cabotegravir, the case 65 R tenofovir rotation mutation is very, very rare. There's only been a handful of cases in 10 years and hundreds of 1000s of people and the majority of those have been in people with undiagnosed HIV at initiation. So the cost of failure with TDF FTC and not finding it sooner is much lower than the cost for cabotegravir. Alright, coming back to logistics, the logistics this is this is a flowchart of our our sort of our flow at Callen Lorde. People probably have other flows that they're trying to develop or have developed. But I think you'll notice you'll, you'll recognize the nightmare of what it's like to, to put this into practice and have a cabotegravir program. So when a patient's interested in our place, everybody gets notified pharmacy gets notified medication support for our financing our billing teams, and we send a prescription into a test prescription to start the prior authorization process. The insurance, our pharmacy runs that claim to see if it's a medical benefit or a pharmacy benefit. And the the prior authorization process for that insurance. If it's a pharmacy benefit, it's simple because we can run a claim and know immediately if the prescription is being paid. But if it's a medical benefit where you're supposed to buy in Bill, that's a nightmare, because if you buy it but don't get reimbursed for it, it's a huge potential risk for health centers, there's a lot of work being done by a lot of places to find alternate ways for medical benefit patients to get the medication from an external pharmacy and bring it in so so clinics aren't taking that risk.

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So the and then the pharmacy has to order it the medication has to be stored, the patients have to be scheduled they have to be notified and reminded. We need tracking systems, you need education systems. You need everybody in the health center to be aware because if somebody is calling to cancel an injection appointment, we need to know that they can't just get the next appointment in two months. They have to get an appointment within a week. So there's a lot of logistics everybody has to know about this program and everybody has to understand the logistics so it's it's a lot going on when we're doing this injection. All right. So now I want to shift to guidance on choosing a PrEP regimen. We now have three options. How do we choose between them? This is from New York State's guidelines and as you can see some of the key factors in the choice of a PrEP regimen are the potential exposure routes. Is it rectal, vaginal, penile or blood? And that will tell you whether which medication you can use. Is it a pill with somebody prefer a pill or an injection to somebody prefer daily daily pills or On Demand or injections? Is there renal dysfunction, osteoporosis, etc. This is another graph of those differences. And as you can see, in terms of the effectiveness TDF FTC actually wins the effectiveness in terms of it being able to be used in all populations, blood exposure and all sexual exposures where there's some caveats with cabotegravir and TAF. cabotegravir sexual only not blood. TAF so only for cisgender males and transgender women the cost we know might be cheap generic for for TDF FTC whereas the other options are much more expensive. Lab frequency is different complicated insurance coverage TDF FTC we can almost always get same day it's it's generic it's cheap insurances love it and we can almost always do same day start TAF FTC. Sometimes yes sometimes no depends on the insurance and Cab LA always an insurance nightmare. On Demand dosing is only TDF FTC side effects tend to be predominantly GI for the orals injection site reactions for camp, renal and bone for TDF FTC metabolic, some weight increase minor but they're for for both cap and Taf same day PrEP, really for TDF FTC mostly, and the tail we talked about. All right, I want to move on to the guidelines. Okay, so New York state guidelines in terms of which PrEP to use. New York state guidelines do recommend

that in the absence of contraindications, clinics, clinicians should recommend TDF FTC as the preferred oral PrEP regimen. But TAF FTC is a preferred regimen for for oral PrEP regimen for cisgender, MSM and transgender women with pre existing renal disease or osteoporosis clinician and but New York State guidelines do recommend cabotegravir LA as a preferred regimen for protection against HIV through sexual exposures for injured individuals who are willing to receive im injections and have no country indications or barriers to its use. Alright, so I want to spend my last few minutes talking about the new testing and monitoring algorithms for for our new medication.

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So let's first talk about baseline testing. The CDC algorithm for baseline testing is rather challenging I find. And if this is basically somebody who's never been on medication, it's not on medication. And they basically have you start with an antibody antigen test. And then if it's reactive, it's reactive. If it's not, then if they have an exposure in the past four weeks, you would do either another plasma antigen antibody test, and or a viral load. And then the thing goes from there, so they're basically doing an antigen antibody test. And then from there, you may or may not do a viral load for initiation. New York state guidelines strongly recommend and put right in there that you should get an HIV RNA assay for initiation. The reason for that is twofold. One is that so we're looking for that window period, right that first month, where an HIV test might not be positive. Now, if we're asking people, whether they've had an exposure in the past months, first of all, some folks are going to be really uncomfortable telling us the answer to that question. And so, you know, if you just get it on everybody, then you don't have to worry about whether somebody's comfortable telling you or not remembers or not that they had an exposure, and you're getting the viral load, which is critical, because the majority of resistance that happens for patients who are on PrEP and develop medication resistance is because they had HIV at baseline and we didn't know it. So getting an HIV viral load at baseline, makes all the sense in the world to us in New York state says please get a viral load as part of your initial HIV testing before starting PrEP. So that's difference number one. What about monitoring while people are on PrEP, it's different for CAB LA than it is for TDF or TAF FTC. For monitoring on PrEP for CAB LA, both CDC and your state, say an antigen antibody tests plus an HIV viral load at every injection visit. Why? Because there's delay detection of HIV antigen antibody up to 98 days, as we said, integration resistance has developed and there was a study presented a Croix this year that showed that actually viral load testing would have prevented the majority of resistance developments cases, so we have a chance to not lose a whole class of drugs for treatment if somebody sero converts well on cabotegravir LA. What about Taf for TDF FTC? Here's where New York State and CDC differ. Okay. CDC has changed their guidelines to say not only should you get a viral load every follow up visit every like three months. Our visit for for so cabotegravir is a is an injection. Every injection is a viral load every injection visit, the CDC says you should also be getting a viral load at every TDF or Taf quarterly follow up visit. And the rationale again is that treatment causes the delayed antigen antibody reaction. But New York State does not recommend a viral load. I mean, I think a lot of places a lot of people, a lot of experts are really questioning why the CDC came down with that recommendation. Given that we've been using Taf and TDF FTC for a decade and we see very few cases of failure with resistance. And when we do it's that 184 mutation. So there's been a lot of questioning about this new recommendation to suddenly start getting a viral load every time you're HIV testing somebody

on oral PrEP. New York State's guideline rationale against HIV RNA testing at every visit is treatment is not caused as significant delay in HIV conversion, HIV antigen antibody conversion, it rarely leads to resistance. When it does, it's the 184 mutation, which does not affect ART choice. And the majority of cases of misir conversions are at initiation and the viral load will capture those folks. So New York State recommends a viral load if somebody comes off of PrEP for a couple of weeks and had exposure during that time, where I was very intermittently adherent, often on PrEP in the last three months. But if somebody is stable on PrEP, the need for a viral load is not felt to be important or necessary. The other place where there's some difference in monitoring ART with STIs and renal function to start with renal function first because it's a little bit easier. The CDC is now saying that kidney on oral PrEP so a Taf or TDF based regimen. If you're under 50. And you start with a creatinine clearance over 90, you only have to get a renal function testing once a year. If you're over 50, or you're sorted out with a brand clearance less than 90, then it's every six months. And if you're on cabotegravir alay, you don't have to worry about renal function. Your state played it a little bit more conservative around this because it feels like a year is a long time to find out that somebody is developing some renal dysfunction on it enough of your base regimen. So the guideline remains every six months and to consider a more frequent screening and those at higher risk. For cabotegravir LA it's at least once every 12 months. The STI story is a little bit strange from the CDC because there if you look at their in their guideline, and you look at their tables under oral PrEP and Cab LA, the guidelines for for STI testing are different. For under oral PrEP, it's for MSM and transgender women every three months for everybody else every six months. But if you look under the Cab LA guideline for MSM and transgender women, it's every four months for heterosexual men and women for gonorrhea and chlamydia it's every six months and for for gonorrhea and syphilis. It's every six months and Chlamydia every year, once a year. So it's a different thing between the two guidelines. New York State guideline just says STI testing for all on PrEP every three months as your starting point like that's the default, get an STI test with the quarterly labs. But you can adjust it based on an individualized risk. If somebody's risk is really quite low for an STI monogamous relationship with somebody with HIV, et cetera, et cetera, then you can adjust that risk. Under Cab LA, the recommendation is since they're coming in every two months if they're our highest risk patients, people with a lot of partners anonymous partners clubs, sex parties, etc. Then get it every time you see them every two months otherwise you can wait every four months. All right, I think that is it. I think I'm within my timeframe updated guidance. So the conclusions are the updated guidelines reflect significant advances in PrEP over the past decade. The new state and federal guidelines mostly agree with some notable exceptions. Cab LA brings in new and exciting but extremely challenging options, the prevention of HIV and access to PrEP continues to be a significant issue for communities most in need of HIV prevention measures. And I will stop there.

[End Transcript]