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ECHO: CABOTEGRAVIR EXTENDED-RELEASE INJECTABLE SUSPENSION FOR PRE-EXPOSURE PROPHYLAXIS

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ECHO: Cabotegravir extended-release injectable suspension for Pre-Exposure Prophylaxis [video transcript]

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Alright, with that I will hand it over to Dr. Urbina. Thank you. Great. Thank you so much. So I'm going to talk about Cabotegravir extended release injectable suspension for PrEP, or Pre-Exposure Prophylaxis. So this was approved last year. And I think it's making its way around both New York City and the state, and just another great tool or option for patients who want to prevent infection with HIV. So these are my disclosures. And the learning objectives, I'm going to review kind of the two in Sentinel trials, the HPT, N Oh, eight, three, and oh eight, four trials that led to the approval for long acting Cabotegravir. And then I think, importantly, we're going to talk about some implement implementation strategies, especially how we're going to roll this out in sexual health clinics. So just briefly, just to talk a little bit, prevention is really a key strategy for ending the HIV epidemic in the US. And just the goal, really, is to reduce overall 75% reduction in new HIV infections by 2025, and at least a 90% reduction by 2030. So we know there's four key strategies, and I'm going to focus in on pre exposure prophylaxis, and how we can utilize these long acting injectables to get to our goals. So I think Jessica had alluded earlier, just in terms of equitable distribution for any intervention. So any new technology or any new intervention is only as good as its equitably distributed. So just to review some of the data here Well, 25% of people eligible for PrEP were prescribed it in 2020. This is data showing that the coverage has not been equal. So overall, we see that, you know, only 25% of those eligible for PrEP have been prescribed PrEP. The vast majority of those are 66% were white, 16%, Hispanic, Latino, and 9%, black, African American. And by 2025, the National Strategic Plan has a key to increase PrEP coverage to 50% from a 2017 baseline of 12.6%. So you see that we have a long way to go. And if we drill in and we look at the distribution, or the who is actually receiving PrEP, and we looked at gay and bisexual men, we see that the percentage of gay and bisexual men using PrEP in the US that there's also disparities. So again, the vast majority of those gay and bisexual men who are accessing PrEP are white 42% 31% are Hispanic Latino, and only 27% Identify are black, African American. So what's new with the guidelines, so these are the updated CDC guidelines. And you know, they um, kind of apply to both oral and to injectable PrEP. But this is what's new in the guidelines. So it's really the addition of viral load testing, along with fourth generation or higher antigen antibody testing, prior to initiation of PrEP, and also at all of the monitoring visits. And the reason for this is based on delayed detection of HIV for persons on PrEP. So someone who is on pre exposure prophylaxis, there's this delayed detection to the Diagnostics Test us to use to detect HIV infection and this delay in detection is greater with the longer acting Cabotegravir. So the HIV antigen antibody can be delayed by 62 and 98 days Um, compared to viral load testing, and that's 62 days delay, if there's a baseline infection and 92 days, 98 days if there's an incident infection. So again, this delay of the antigen antibody test compared to viral loads, and that's for intramuscular CAB. Oral Pre-Exposure Prophylaxis also has this delay. And it can be anywhere from 34 to 31 days for baseline and incident infections compared to viral loads. So again, both oral and intramuscular have this delay detection. But the magnitude of this delay is greatest with the Cabotegravir. So just looking at some of the updated CDC guidelines, so I so again, this is for guidance regarding Cabotegravir. So we know that identifying patients that are at increased risk for HIV, so it's a no

or vaginal sex in the past six months with any of the following. So either an HIV positive sexual partner or if their HIV status is unknown, a bacterial STI in the last six months history of inconsistent or, or, or no condom use, but also persons who inject drugs, in particular, if they have HIV positive injecting partner or if they're sharing injection equipment. So all of the conditions need to be met prior to initiation. So documented negative antigen antibody test, within one week before initial Cabotegravir injection, also negative viral load tests, no signs or symptoms of acute HIV infection, no contraindication. And we're gonna go over some of those, and then we'll talk about the dosage. So it's 600 milligrams of Cabotegravir, as administered as a three ml intramuscular injection in the gluteal muscles. So you have an initial dose, and then you have your second dose, same milligram administered one month after that first dose, and then it's every eight weeks thereafter. And again, at every follow up visit. And even one month after that first injection, you're going to perform both antigen antibody test and viral load testing. And then at follow up visit every two months or beginning with a third injection, again, antigen antibody testing and viral load testing. Again, for those that are injection drug users, you also want to have access to clean needles, syringes, or know where to refer patients for that. And then again, really PrEP opens the door to talk about sexual health and screening for sexually transmitted infections. And we'll go over a little bit later the frequency of testing but at follow up visits every four months is when you really want to do bacterial STI screening for men who have sex with men and transgender women who have sex with men. So that's oral, rectal, urine, and then blood for syphilis screening. And then at follow up visits every six months. You want bacterial STI screening for all heterosexually active women and men. So that's vaginal rectal urine. Also blood testing and then at follow up visit at least every 12 months. You want to assess for desire to continue on Pre-Exposure Prophylaxis, but there are also chlamydia screening for heterosexual reactive women and men. So again, at every point at the follow up visit, you want to re-educate patients about the tail. long acting Cabotegravir has a very long tail with treatment discontinuation up to a year and longer assess for ongoing HIV risk and prevention. And again, if PrEP is indicated if they have an inter option then to bridge with oral PrEP. Okay, so fortunately, with the long acting Cabotegravir, there are a few drug drug interactions, but there are some so the riffa meistens they are inducers of the cytochrome P 450. And they may lead to decreased levels of Cabotegravir Rifabutin may have a similar effect, but somewhat less than

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the other rifampicin. And then luckily, the data looks like for both hormonal contraceptives and also for feminizing hormones doesn't seem to be a significant drug drug interaction and can be safely co administered. And then for the anti seizure medication. Similarly, the Carbamazepine the oxcarbazepine Phenytoin Phenobarbital they are contraindication because they may reduce the drug levels. So here's the timing of of CAB PrEP associated laboratory tests, you don't need a lot of laboratory testing so you don't really need to monitor for liver or for nephrotoxicity. There, is a good practice to do these at baseline and annually, but really HIV testing which is both the combination antigen antibody and viral load at initiation along with STI screening, and then you're going to repeat the H the HIV testing really at every visit prior to an injection. At q four month you're gonna do bacterial STI screening for men have sex with men and transgender women. At q six month you're going to do bacterial STI screening for heterosexual active women and men only. And then for heterosexual the active women and men only q 12

chlamydia screening. And again when you stop Cabotegravir. You also want to repeat HIV testing, antigen antibody viral load, but also screen for STIs. So I spoke a little bit about this tail. So what happens is that when the drug is stopped or interrupted, if they don't come back for their repeat injection, what happens is that these drug levels start to decrease. As these drug levels decrease, they reach a threshold to where they are no longer protected against acquisition of HIV. However, they are still the drug levels are still present at detectable levels. So what that means is that patients are no longer protected against HIV infection. And if they do sero convert, they're at greater risk because of this low level. Drug levels of Cabotegravir to develop resistance specifically entered race, strand transfer specific resistance. That's why for patients if they interrupt therapy, you really want to have counseling and education about the importance of taking a tale of oral PrEP for a year. So just to briefly discuss the HPTS O, eight, three and O eight four studies. So these were phase two B three randomized, double blind, placebo controlled international trials. The O, eight three study really enrolled men who have sex with men and transgender women and the O eight four trial, enrolled cisgendered women, they both had this old oral lead in with either oral CAB or oral TDF FTC versus placebo. This was double blind double dummy. And then the patients either received active Cabotegravir or active TDF FTC. And really, their main primary outcome was to look at any HIV sero conversions. At the end of the study on there was an open label extension. And patients. were then put on oral Pre-Exposure Prophylaxis, they also looked at incident HIV infections, they looked at grade two or three adverse events. One of the important findings from the study was that there was no significant adverse events would be oral lead in, or with any of the Cabotegravir injections, so no hypersensitivity reactions related to study drug in the phase two or three. And that's why now that oral leading is optional. And again, at Sinai, really, we're I mean, a lot of our patients, we opt not to start with the oral lead-in and and go direct to inject, and there were no serial conversions when resistance was seen in this tale phase when patients interrupted the long acting injectable. And really, the CAB arm demonstrated superior efficacy to the oral Pre-Exposure Prophylaxis. Therefore both of these trials were ended prematurely following the DSMB recommendations and they did meet superiority over oral PrEP. And importantly, these residual concentrations of Cabotegravir may remain in the systemic circulation for up to 12 months or longer. So it's important that patients that are an ongoing risk for HIV infection if they either should interrupt therapy have a planned interruption, that you have counseling and education about the importance of of a tale with oral pre exposure prophylaxis. So again, superior efficacy to oral PrEP. And again at the end of the study, here offered oral Pre Exposure prophylaxis. So just some of the important baseline demographics, and the oh a three is that they had about 12 point, around 12% of patients that identified as transgender women, the mean age was 26. And close to half of the participants were black African Americans. So the study recruited a large proportion of transgender women, young persons, and black African Americans, which is really representative of those newly diagnosed with HIV. And in the OIC, for study. Most of the women were young of about 57% were less than 25 years of age, they were at higher risk for HIV, as noted by the number of sexual partners and this medium voice score, which is a kind of risk based score that predicts risk for HIV. And we also saw high rates of STIs. And importantly, to 99% of participants were not white. So looking here at the Kaplan Meyers outcomes here of oral TDF FTC vs CAB, on the horizontal axis, and on the vertical axis was the cumulative incidence for HIV infection. What this graph shows that there was a superiority of the long acting Cabotegravir and a risk

reduction of 69%. And in the OIC, for study, similarly, they showed a superiority for the long acting Cabotegravir. And in this case, that risk reduction was 90%. So at each of the time points, it's important the HIV testing that was performed. They performed rapid HIV testing lab based fourth and fifth generation HIV immuno assays and quantitative viral loads. So that was that screening. And then for enrollment, what they did was a rapid HIV and a lab based fourth or fifth generation HIV immuno assay. And that's what they did at each of the study visits. But and then they stored samples for further testing in the event that a positive at any positive point. And then what they would do is at the first moment, at that first laboratory visit where there was a positive HIV test, then they went back to previous samples, they did more testing, looking at qualitative RNA testing, single copy RNA testing, resistance testing and drug concentration levels, to better time the point of HIV infection. Remember the importance of viral load testing, and what was demonstrated in this study is that there wasn't delay time to detection, just using antigen antibody testing, and that by utilizing viral load testing, you were able to pick up infections earlier, even up to four months, in some cases. So there were breakthrough infections, there were 12 in the cabotegravir arm, and there were four that a cure that occurred even with ontime Cabotegravir injections. Hover contrast that to 39 per that occurred with the oral PrEP arm. Similarly, with the o eight for study, there were three serial conversions in the CAB arm compared to 36 in the oral PrEP. And one of these that occurred even with on time injections, and there was some breakthrough infections where resistance

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also occurred. So again, with the CAB 12 incident infection, there were five that had some resistant associated mutations. Four of these were integrase strand transfer associated mutations and contrasted to the 39. On oral TDF FTC, there were 11 resistance associated mutations, and four of these were nucleoside reverse transcriptase mutations, but all these patients with incident infection really retain full options for fully active regiments, and that's important. So in the OAIC, for they had three incident infections in the CAB arm, no resistance associated mutations, and in the oral PrEP that were 36 infections, nine resistant sation mutations, with One NRTI associated mutation. The major side effect from these medications from the long acting was really the injection site reactions. So these occurred with greatest frequency, and the other ones really didn't differ too much from the oral TDF FTC arm. So the big real side effects or adverse events are these injection site reactions. Luckily, these injection site reactions tend to diminish over time. So if we look at the frequency of these injection site reactions divided up by mild, moderate and severe, we see that in all cases, really, there's a reduced frequency of these injections over time. However, when they do occur, the most common injection site reactions where pain and tenderness followed by nodules in duration, swelling, bruising, erythema, and pruritis. So these were the most common side effects the injection site reactions again, they decrease over time, and in very few cases, lead to treatment discontinuation. In fact, 2.4% of patients in the OA three, study discontinued due to the injection site reactions, I think a big concern with integrase inhibitors this this concern for weight gain, which we've seen with the oral second generation integration inhibitors, what we saw here and in this graph here, you'll see the CAB arm. And then you'll see that TDF FTC arm TDF FTC is anorexigenic. So in the beginning, what was noted was a decrease in weight in the TDF FTC arm and about a 1.26 kilogram increase in weight. So there was an initial immediate increase in weight in those in the CAB. But later, there were similar increases in weights across both arms

that did not differ. So there was no significant differences in weight gain between the CAB and the placebo. And participants in both groups gained approximately one kilogram over the course of 41 weeks. So I think this is encouraging that it may be a little bit more weight neutral. So again, just going over how to dose the medication, this oral optional, lead in with oral cabotegravir, your 30 milligram tablet once a day for that first month. Then on that final day of the optional lead in or within three days is when you give the first 600 milligram injection. One month later, you give the second loading dose. And then at month five and beyond all subsequent injections are then every two months. Again, no real concerns in terms of drug drug interactions, hepatic or renal dosing, there's really no dose dose adjustment required. And again, from mild to moderate creatinine clearance, they do recommend increased monitoring for those between 15 and 30, or for end stage disease and again, very little pharmacokinetics for end stage renal disease including patients on on dialysis, if you do decide to go straight to inject, you're going to do your testing within one week of that you give your first loading dose, one month later, you give your second loading dose, same dose, and then month four and beyond. It's every

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few two months.

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So the way that you really want to plan and implement long acting Cabotegravir because really adherence to the injection dosing schedule is really strongly recommended you want to choose a target injection date, and the injection should be given on that same date every two months. Consider the first to the 28th has not all months have an equal number of days and then you basically have a plus or minus seven day window and injection should remain as close as possible to the target injection date. Subsequent injections should really return to that target injection date or as close as possible. So let's talk about some of the scenarios here. So for plant interruption, so you can bridge the medication and you can bridge with oral Cabotegravir for you know, up to two months. You can bridge with other oral preps for longer if if need be and what's Important is that if a dose is missed of the next injectable, and if it's less than a month, then you continue with the every few two month injection. If it's been greater than a month, then you have to reinitiate the injections with the two, three ml 600 milligrams one month apart. So here's a patient, optional oral lead in loading, loading injection, and then they're going to miss their next dose, which should have started at month seven, they're taking an oral bridge, because it's been more than a month, since their last injection, you got to reload them with the two loading doses, and then you can continue with the Q two month. Here is a case where you are bridging, but it's less than a month. So injection, injection, injection, and then they have a plant interruption. But its own it's, it's less than a month. So you can just resume with the queue, two months dosing. So again, really, it's that plus or minus a month from their next plant injection is where is where you decide if you're gonna if you're gonna have to redo loading doses, or just continue with q2 months. And lastly, here, I just want to touch on implementation or process flow and its sexual health connects. So for initial labs, again, you want to do the lab base, fourth generation, antigen, antibody and viral load. And then with that first injection within one week of those labs being resulted. I think a good practice is to do a comprehensive metabolic panel pregnancy tests urinalysis screen for hep a, be doing the full panoply surface

antibody, core surface antibody, and core antibody to hep C with the reflex to HCV, PCR and then RPR, three site GC, Chlamydia, and then annually to repeat, a set of lights, urinalysis and Hepatitis C, if at risk, and then for their maintenance. dosing. Remember, just prior to every visit, you're going to have to have some documented negative HIV test. And what the CDC says is that this HIV test can either be a rapid point of care, or it can be a fourth gen lab based testing. Remember that in addition to these two, or you are also going to have to draw a viral load, but you can inject prior to that viral load being resulted. And then again, I think we went over the frequency for the STI testing based on risk for q4, q six, and

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q12.

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So what's important to remember is that prior to any injection, you need to document a negative HIV test, it can either be a rapid point of care, or a lab based fourth generation test. And you also need to draw a viral load. So I think you could have two flows, one of them could be if you're going to inject on that same day. So again, I think the flow would be that for prior to initiation lab based or Gen anti antigen antibody viral load, within one week of that, you're going to give that first injection at month one to and remember, prior to every visit, you're going to have to document that the patient is HIV negative. So if you want to do it, same day, you can do point of care, rapid fourth gen if negative, then draw viral load and inject. If your flow is different, or you don't have access to rapid point of care testing, then you're going to schedule the lab base fourth gen antigen antibody and viral load and then schedule a follow up visit within a week of these for that follow up injection. So again, I think CAB long acting was superior to oral TDF FTC for prevention of HIV infection and transgender women. cisgender men have sex with men and cisgendered women in clinical trials. It was well tolerated really no drug related hypersensitivity reactions during the oral lead-in and few patients withdrawing due to injection site reactions, but again, I think what's important with implementation is adherence to the subsequent injections, making sure that we can identify virologic break throughs serial conversions and put patients on a fully suppressive regimen or if they interrupt is to put them on an oral Pre-Exposure regimen for at least a year and or longer if they're at ongoing risk. So I will end there.

[End Transcript]