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IS HIV THERAPY GOOD ENOUGH OR DO WE STILL NEED NEW DRUGS?

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Joel is going to talk to you about a topic that he knows quite a bit about. He really has been one of the people who has been involved in the clinical development of almost all the anti-retroviral agents that we have that are approved at the present time and he's going to talk about why we may need some more. So, Joel, without further ado if you would take it away.

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So, I'm going to talk about whether we still need new drugs.

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Here are my objectives.

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Here are the DHHS guidelines. If you look at the top box you know almost everything is an integrase inhibitor with the one exception of Darunavir.

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And then if you look at the IAS-USA guidelines, they took a more minimalist approach and really narrowed it down to, you know, what are the drugs we would really use. So, I just wanted to point out that all of the recommended regimens in the IAS-USA guidelines do contain integrates inhibitors and all but one use TAF as the nucleoside, the exception of course being Dolutegravir and Abacavir-Lamivudine. So that's pretty good. We've got a small handful of regimens that we use frequently that have a lot of very positive attributes.

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These are the characteristics of ARV regimens and I want to go through them and talk about, you know, how our current regimens stand up with respect to these attributes and where there's room for improvement. So, efficacy and durability, convenience, tolerability, toxicity, resistance barrier, activity against resistant virus, drug interactions, testing requirements, and cost.

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Let's start with efficacy and durability and I would propose that we're not going to be able to do much better with new drugs than we're doing now.

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If you look at some of the recent studies the SINGLE study comparing Dolutegravir plus Abacavir 3TC with Efavirenz. This was of course the first study that showed superiority over Efavirenz, which had been the gold standard. 88 percent versus 81 percent at 48 weeks.

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Now, what was this efficacy based on, this superiority based on? Well, it wasn't really a virologic difference. Virologic non-response or virologic failure occurred in very few people and was no different between the two. So, the difference was really in discontinuation due to adverse events.

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If we look at an even more recent study. These are two studies comparing E/C/F/TAF versus E/C/F/TDF, Genvoya versus Stribild respectively. And in this case again virologic failure was very low but by 144 weeks, there was superiority of the TAF-based regimen over TDF-based regimen. And again, that was based not on virologic differences but on the fact that more people were discontinuing TDF due to toxicities. So, efficacy is really good now. We're starting to see studies where failure is occurring in 5 percent or less. And a lot of those failures are people who are not taking their medications or who drop out for various reasons. So, it's unclear that new therapies are going to be better from an efficacy or potency standpoint.

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What about convenience? Well we're doing pretty well with that too. These are the IAS-USA recommended regimens. I picked these guidelines because it's the smallest number, but you can see that there's a number of these are single tablet regimens. Almost all of them are single dose regimens. The exception being Raltegravir, although we'll soon have a 600 milligram once daily formulation of Raltegravir. And the number of pills ranges from one to three per day. So that's quite an improvement over the way things were in the earlier days.

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Even for treatment experienced patients we're starting to see improvements in convenience. So, these patients who were on very complex salvage regimens until recently because of the combination of medications can now be treated with fairly simple regimens. This is the best example I know of, the GS 119 study, which took patients who were highly treatment experienced, had experienced at least two prior failures and had at least two-class resistance. The exceptions were they couldn't have integrase resistance, they couldn't have primary Darunavir mutations, and they could have no more than three thymidine analogue mutations or TAMs. And those people were randomized to stay on their current regimen or to switch to a two pill a day regimen of ECF TAF, again Genvoya plus the 800 milligrams of Darunavir or Prezista.

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Here are the baseline characteristics and I show this slide only to focus on what people were on before they enrolled in this trial. The median number of pills was five per day and about 40 percent were on six or more pills per day so they were randomized to switch to a two pill regimen. And as we now know at 48 weeks the switch regimen was superior to the original regimen and that included superiority in terms of virologic failure. So not to say this is the only regimen. That's an example. Nor can this be used in all salvage patients because of those mutation restrictions. But it does show that the people who were on these very complex salvage regimens for many years can now be put onto some simpler regimens.

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What's coming that may further improve the situation? Well, we have DCF TAF coming. This is the Darunavir-Cobi with FTC TAF. This will be the first single tablet PI based regimen. We have a Bictegravir FTC TAF, which I'm going to talk about. This will be the first single tablet regimen involving an unboosted PI with TAF FTC. We have once a day Raltegravir. They won't be a single tablet. In fact, it's still going to be a three pill a day regimen but at least it's once a day. There's Doravirine, I'm going to talk about later with coformulated with generic TDF and 3TC. Cabotegravir/Rilpivirine, and other long-acting agents that are being looked at. So in terms of drug development a lot of what's happening is trying to improve convenience and possibly decrease dosing frequency.

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Let's talk about Bictegravir briefly. This is a new unboosted integrase inhibitor that will be coformulated with FTC TAF. In fact, that may be the only way it will be available is in that three drug combination and it's been compared with Dolutegravir plus FTC TAF in a phase 2 study where it showed comparable comparable efficacy. This is too small of a study to talk about statistical superiority or non-inferiority. So, although it looks like there's a difference in efficacy, really you can't say that because of the small numbers. But probably in Paris this year at the IS meeting we'll hear there are now four different phase three studies fully enrolled and we'll probably begin to hear results this summer. So, this looks like a very promising agent so far.

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LATTE is a study looking at intramuscular injections of long-acting Cabotegravir, which is an integration inhibitor plus Rilpivirine, the NNRTI that we already know about. And in this study people were already suppressed on anti-retroviral therapy and then were randomized to switch to either monthly dosing or every two month dosing or to continue oral therapy. And overall the results looked the same. However, there was a little more failure and the resistance that occurred all was in the every two month arm. So, going forward they're going to be studying this for monthly IM injections.

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Here are the results again at week 48. And again, you can see down right here that there was a little more of virologic nonresponse with every two month dosing compared to either oral or monthly dosing.

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And then this is MK-8591 long-acting and NRTI that has been looked at just in single dose studies but looks like it may have the potential to be either a parenterally administered or an orally administered agent with long dosing intervals. So, this this also looks promising and of course when you are developing long-acting drugs it's not enough to have one drug because you need a full regimen so you need to have the ability to partner your drug with other drugs that can be given long-acting and now there are quite a number of candidates in development. I suspect that the Cabotegravir/Rilpivirine combination which looks very promising but still it is a deep two injections in the butt every month with some injection site reactions. I think it's a start but of course we're all hoping that future long-acting therapy will either be oral or subcutaneous and a little less onerous for the patient and the staff.

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And then there's also interest in not just injections but implantable devices. So, for example here are some subdermal implantable devices that are being looked at to deliver TAF. And I don't know the technical details of these but the idea here is that you would inject these and you would implant these and they could be refillable. You know one of the concerns with injections and it may apply to these as well but that is the so-called tail that if you give somebody an injection of these medications and they miss a dose, meaning they don't show up for their monthly injection, they're going a month with slowly declining subtherapeutic levels and it could be a recipe for resistance. So, people are trying to look at other ways where you wouldn't have so much of a tail and there would be less concern about that. I personally think they should make these devices so that when they get empty they start to itch and then people have to come in because they've got to. I don't know if you do that. Or it turns blue or something.

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All right what about tolerability? Well again we're doing really well with tolerability. Here is the ACTG 2557, which I think is the most important of many studies that show that integrase inhibitors are kind of the way to go. This was comparing Raltegravir, boosted Atazanavir and boosted Darunavir. And from a virologic standpoint there really was very little difference in the three. But if you looked at tolerability failure, people coming off therapy for tolerability reasons, then you start to see a difference.

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And if you combine those two endpoints both virologic and tolerability failure then Raltegravir looks best, Darunavir in-between and Atazanavir was the worst. Mostly for bilirubin reasons and things like that, not serious problems but there was more gastrointestinal side effects with both of the protease inhibitors than compared to Raltegravir and more with Atazanavir than Darunavir. And there have been many other studies now that really show better tolerability with integrase inhibitors than with comparators, including Evafirenz and boosted PIs.

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We've also seen a number of switch studies a long list of switch studies to TAF from TDF and other regimens. This is the 109 study where people who were on either Evafirenz, boosted Atazanavir, or ECF TDF were switched to ECF TAF and overall the switch was superior to staying on therapy and that held for people who are switching from Efavirenz or from Atazanavir. Superiority mainly of course based on tolerability.

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What about toxicity?

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Well here are the drug toxicities that some of you are probably too young to even remember but if you do remember them they can be pretty awful. And frankly when we started people on anti-retroviral therapy say in 1996, even though we knew we could suppress their viral load and save their lives, we

also knew that the clock was ticking. That they were going to, no matter what we did, they were going to develop some long-term toxicities that we were going to have to deal with. It wasn't a question of if it was a question of when. So that included metabolic toxicities with some of the early PIs, including insulin resistance and hyperlipidemia, neuropathy with all of the D drugs, the early nukes, lipoatrophy with virtually all of the early nucleosides, the occasional hepatic steatosis and lactic acidosis with the early nukes, CNS toxicity with Efavirenz, nephrotoxicity with Indinavir and TDF, and bone toxicity with just about everything, but TDF being a little worse than than the rest. And frankly we don't have to deal with any of these anymore, at least not as inevitable consequences of therapy. It's not to say some of them don't still occur. But there are drugs we can put people on now that they can probably tolerate for a long long long time.

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TAF has been an improvement clearly over TDF. And the mechanism is that although they both turn into Tenofavir, you get about 90 percent lower plasma levels of Tenofavir with TAF than you do with TDF and that's those plasma levels that are thought to be contributing to the nephrotoxicity and the bone toxicity of TDF.

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And you know rather than go through all these studies which I'm sure other people will discuss in the course of this conference, here's a summary of all of these many switch studies to spare you all the details. But here's the bottom line: results that in general TAF is either non-inferior to TDF or in some cases superior, and I've shown the examples of where it's superior. You see an increase in bone density, which we assume will translate into less fractures although we don't know that for sure. And you see either a stability of the GFR or in a couple of cases an increase in GFR after the switch with no tubular toxicity described so far. And overall a decrease in proteinuria both overall proteinuria and the tubular proteinuria that we see with TDF. And again, that is assumed to mean that there is greater renal safety. These are all surrogate markers so we have to be careful but they're pretty good surrogate markers so I think we can we can safely say that TAF has better renal and bone safety than TDF.

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And here I'll just show an example of one of the studies in terms of toxicity when you switch from F/TDF to F/TAF. Again, that's Truvada to Descovy. You can see that proteinuria goes down in green on the right whereas if you stay on TDF your proteinuria increases. Now these are not necessarily clinically significant levels of proteinuria. But the fact that people who have been on TDF and stay on TDF continue to have slow increases could tell you something about the long term renal effects. And this is just sort of overall proteinuria, the albumin creatinine ratio, the retinal binding protein and beta 2 microglobulin are considered to be markers of tubular toxicity which is the specific tenofovir toxicity. And over here you see a rise an estimated GFR with the switch.

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And then bone changes. Now remember in these studies people have already been on TDF for a while. So, they've all already experienced that drop in bone density that you see in the beginning when you

start people on TDF. That's why when they stay on TDF it just stays flat because they've already had their reduction. But when you switch to TAF, you see that over one year and then again over two years you see a steady rise in estimated GFR-- I mean, sorry bone density, I think it remains to be seen whether or not you'll get back to baseline. We don't know yet whether you will restore all of your bone that you lost when you started the TDF or not but clearly, it's a good thing to have increased bone density.

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In terms of TDF to TAF switches I think the advantages are clearly the increased GFR, decreased proteinuria, improved bone density, and for what it's worth it's a smaller pill. Disadvantages well, TDF is a lipid-lowering agent. No one knew that when they developed it but it turned out to be one. And so you do get a decline in lipids and when you reduce plasma tenofovir levels by 90 percent of course you lose that effect. So, a lot of people think that TAF increases lipids. No, doesn't increase lipids it just doesn't decrease them the way TDF does. Not to say we should be using TDF as a lipid-lowering agent. We have statins for that. And they have shown a demonstrated clinical benefit whereas TDF, we don't know that it makes a difference. And of course, the other big difference is that TDF will be generic before too long. And at some point, the price is going to go down and TAF will become more expensive. Right now, it's not but when it is we're going to have to decide probably not individually but as a society whether we still give the more expensive TAF to everybody or whether we restrict it to people who have evidence of TDF toxicity. Currently the IAS-USA recommendations say if there's no increase in price then switching from TDF to TAF is reasonable even if the patients are not experiencing TDF toxicity.

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All right. So, what about resistance barrier?

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As you've heard earlier we of course we know that boosted protease inhibitors have very high resistance barriers. Essentially nobody develops resistance on a boosted PI if they don't already have PI resistance and are taking it as an initial regimen. And it looks like Dolutegravir is close to that if not on par with that. In contrast, the other integrase inhibitors that we're currently using, which are Elvitegravir and Raltegravir, you can develop resistance and not that it's common but that you know when you when you fail you can fail with either single or multiple mutations that cause integrase resistance.

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And of course, NNRTIs are generally thought to have about the lowest barrier to resistance. They've been excellent choices for us over the years in that especially with Efavirenz they had very long PK so they're sort of pharmacologically forgiving. But if somebody has frequent dose treatment interruptions due to non-adherence that's where you commonly will see in NNRTI resistance. That can be, you know, can cause resistance to multiple drugs in the class. So, we're doing better with resistance barrier if you think about both the IAS-USA guidelines and the DHHS guidelines. A number of those regimens especially the Dolutegravir and Darunavir-based regimens have very high barriers to resistance, which is important in treating people who may be non-adherent.

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Now we have recently seen a case, the first case report, of somebody who may have developed Dolutegravir resistance despite on first line therapy and this was just reported at CROI. A 45-year-old man with PCP came in with acute retroviral syndrome, was started on a Dolutegravir regimen and discharged then readmitted to the ICU several days later with hypoxia that was thought to be an IRIS reaction to PCP but during hospitalization the viral load was going up despite directly observed therapy and they were able to look at drug resistance over a period of days and documented very rapid evolution of integrase resistance. So, you can see multiple important integrase mutations. Now the one weakness of this study was that they didn't do a baseline integrase resistance testing and none of us do. I mean, it's not recommended there's no reason you would need to do that but obviously for the purpose of reporting this case it would have been nice to know if the patient had had any integrase resistance at baseline that was just being selected or whether this was true selection. But without knowing that, I would say this is the first case where it looks like probably there was selection of and emergence of integrase-resistant virus. Should we be panicked? Should we be nervous? I mean the fact that it's taken this long to hear of such a case tells us just how high the barrier of resistance is to Dolutegravir. And I think in fact this case is almost more reassuring than scary because if it was a common thing we would have heard about it years ago, given so much Dolutegravir use.

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What about activity against resistant virus? Well this is less important when we're starting patients on therapy because most of our patients don't have resistant virus but it is of consideration especially if patients have failed or for our patients who have treatment experience.

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What's coming? Well, Bictegravir we talked about already and it's in-vitro looks even better than Dolutegravir in terms of its activity against resistant virus. It even has some in-vitro activity against Dolutegravir-resistant virus and Dolutegravir has activity against resistance to the other two integrase inhibitors. So, promising, but again how many people really is this going to affect? We don't have a whole lot of Dolutegravir-resistant patients. Ibalizumab. That's one of my favorite drug names. I like to say it so much that I'm gonna say it again. Ibalizumab is a monoclonal antibody that binds to CD4 receptor which blocks-- it doesn't block attachment, attachment is already current-- it blocks post-attachment entry. It's given by I.V. infusion every couple of weeks. Not attractive. But if you have one of those rare patients with untreatable virus this is a big hope. And it's actually, despite the need for I.V. infusion, it is very well-tolerated. And then we have Fostemsavir, which is a true attachment inhibitor and there are quite a number of patients in the U.S. now who are getting the combination of Ibalizumab and Fostemsavir, two brand new classes for them, who had untreatable virus before and are suppressed. So, this is promising for a select group of patients. Usually when I ask people at HIV clinics how many people do you have with sort of untreatable virus, the answer is always either 0 or 1. So it's not a huge market but if you're one of those patients it's very important. And then we had a maturation inhibitor but that has both been withdrawn from further development. There may be other maturation inhibitors but this one is not going to go forward.

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Just coming back Ibalizumab because I wanted to say it again. This is a study presented at CROI where they took patients who were not suppressed on their current regimen because of drug resistance. They had to be resistive to at least one drug from three different classes and they had to be sensitive to at least one agent so that when they used Ibalizumab it could be combined with that second drug because you obviously don't want to give this by itself. And it was given as a monotherapy infusion on top of their existing regimen and then at day 14 they switched over to the new regimen. Fifty three percent had resistance to drugs from from at least three classes and 68 percent had integrase resistance.

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And here are the results. The primary endpoint 83 percent had at least a 0.5 log decrease at day 14. So, remember this is looking at that monotherapy period. So, you're really looking at the effects of Ibalizumab alone, compared to 3 percent in the control arm and you can see that about half were were fully suppressed. There were very few serious adverse events. Of course, this is a very sick patient population so it's not surprising that there were deaths, but not felt to be due to Ibalizumab.

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And then Fostemsavir. Again, this is the attachment inhibitor. And in this study a similar kind of patient population was given Fostemsavir with Raltegravir and TDF, an unusual backbone but that was what they chose, in various doses compared with boosted Atazanavir.

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And 90 percent of patients had undetectable viral loads at week 96 and it was it was quite well-tolerated. So again, two drugs with entirely new mechanisms of action that inhibit viral entry that look promising for people with drug resistance.

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What about drug interactions?

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Well of course we're very familiar with Ritonavir and Cobicistat interactions. They've generally been the ones we've had to deal with the most. And I do think that as we go forward the need for boosting is going to go down. We'll still probably be using it in certain treatment experienced patients but very few I think in the future very few treatment naïve patients will be on a boosted regimen, which will of course decrease drug interactions.

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I've listed a few here. I would just remind people there's only one drug I can think of that people can buy without a prescription that you have no control over that can interact with Cobi and Ritonavir and that's Fluticasone nasal spray. You also have very little control over the things that orthopedic surgeons will do to your patients and inject into your patients. So, you know, be careful. When Fluticasone went over the counter all of the HIV doctors kind of turned pale and got sweaty because it's a serious interaction and

now people can get it anywhere and everywhere and sure you may educate them about it in the fall. But by the spring when the pollen comes out they will have forgotten your message. So just remember that if you're if you're using a booster.

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What about testing requirements?

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First of all, I talked about this before, do we need to be checking for integrase resistance at baseline? And this keeps coming up, you know what does add cost to the test. It hasn't been standard. But frankly transmitted integrase resistance and in fact all integrase resistance remains very uncommon in the US. The CDC survey of the prevalence overall of integrase resistance was .4% but it was a tenth of that for baseline transmitted integrase resistance. .04%. You certainly aren't going to spend hundreds of dollars on a test if only .04% of people have resistance. It was a little higher in the in the University of North Carolina cohort but still quite low. And there was a modeling study where they, assuming a .1% risk, which is higher than what they saw in the CDC, and a cost of $250 per test. They actually estimated that if you were to do integrase resistance testing, it would not only be associated with higher cost but worse outcomes. And you say well how could a test give you worse outcomes other than a bruise on the arm? Well, it isn't that. It's that a lot of those mutations that you'll pick up if you do testing are polymorphisms that really have no significant effect on integrase activity. So, if you end up putting somebody say on a boosted PI when they would have done well on an integrase inhibitor, because of polymorphisms you may have more side effects and more toxicity and that's where they came up with that worse outcome measure. So, the bottom line is you don't need to do it. There may be situations where you would say somebody who comes in and their baseline genotype shows lots of nucleoside and NRTI and PI mutations, you might want to then check them for integrase mutations as well since your options have become restricted. But in general, it doesn't need to be a standard test. Now the other point of testing requirements is what do you need to do both on therapy and before starting? And one of the things about the new drugs we have is that there's less of a need for some of that testing.

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And I want to focus on the UCSF experience, which is now being replicated all over the place and that's the idea of rapid start where you start patients the day they're diagnosed. So, people in the early days where we had CD4 guided therapy it was sometimes a long time, in this case I believe these are are weeks, a long time before people were suppressed. Then we started doing universal therapy based on regardless of CD4 and you shorten that gap. But now with rapid start-- I'm sorry, this is days-- with rapid start you can get down to undetectable viral load very rapidly. And this does two things. I think one, if people leave the clinic with a prescription rather than with four appointments to meet with this person and that person and the other person, I think they feel more engaged in care. Most of them. Some of them need time to process. But some of them are feeling like something is being done. And the second of course is that many of these people may still be engaging in high-risk activity, so you're reducing transmission rather than waiting and letting them transmit HIV. So, in our clinic if a patient comes in to see a case manager, just been diagnosed, referred from the health department, case manager chats

with them for a little while and says, "What would you think about starting today?" and if the patient says, "Oh yeah, I'd like to do that," they pull me or another provider into the room to say this is so-and-so. He doesn't take any other meds. He's interested in starting. We start. We draw the labs of course but we don't need to wait for them.

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Now. The deal is you can't do that with every regimen. There's only a few regimens you can do that way and these are the ones that I've come up with. Dolutegravir plus F/TAF two pill a day. ECF/TAF one pill a day or Darunavir Cobi plus F/TAF one pill a day. You have to avoid certain drugs because you do need test results. For Abacavir you would need an HLA B*5701, for TDF you need to know the renal function, for Rilpivirine you need to know their viral load and CD4. And really for an NNRTI you need a genotype because that's the most common type of transmitted resistance. So, something to think about. It really involves some workflow changes at clinics but it's being widely done and the patients seem to like it.

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Finally, cost. So, I saved the most difficult for last.

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We've been looking at a lot more of these two drug regimens. And initially I think two drug regimens were mostly designed to avoid nucleoside toxicity they were so-called nukes bearing regimens. But now we're not as worried about nukes toxicity anymore it's not really a driver. What about reducing cost? Well for some of the two drug regimens, especially the ones that contain Lamivudine, that's a potentially cheap generic drug that could really reduce costs. And then of course the other rationale for two drug regimens is to allow for longer acting therapy.

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Recently we saw probably the best study yet of two drug regimen presented at CROI. This was the SWORD studies where people who are on suppressive therapy were randomized to stay on therapy or to switch to Dolutegravir Rilpivirine, a two drug regimen that can be given today. Again, very low rates of virologic nonresponse. Remember these are all people who are suppressed so they're presumably adherent. And really no difference overall in terms of anything. There was one patient who had virologic withdraw at week 36 with a NNRTI mutation, the 101 E. That patient was documented to be non-adherent. Actually remained suppressed on that regimen, had no integrase resistance. But otherwise there was no emergence of resistance. And there was a little more toxicity with the switch. Not surprising when you switch over to two entirely new drugs that you might have more. But it didn't affect the overall outcome. So very interesting. The only issue here is that this is, although it sounds like a simple streamlined regimen, in fact Rilpivirine comes with some baggage. It has to be taken with a meal, you're not supposed to use it with high viral loads or low CD4 counts, you're not supposed to take proton pump inhibitors. So, for a patient who's taking a one pill a day regimen that can be taken with or without food once a day and they have to switch to this, it may not feel streamlined to them. The fact that there's only two drugs in it instead of three may not really register with somebody who's taking one pill a day. So, you have to keep that in mind. But it does look like so far, I would say of the two drug

regimens we've studied this is by far the one where we had the best data. Though again it's a switch strategy not a naive strategy. And in this case most people were on TDF and of course they're coming off TDF, so not surprisingly bone turnover markers improved with the switch.

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And we have, I think, even more intriguing is the Dolutegravir Lamivudine two pill regimen. This has gotten a lot of enthusiasm for very little data but it's certainly promising. This is the Argentine study done in 20 patients and this was a regimen where they actually started it from baseline. They didn't switch. So, they weren't suppressed. They were supposed to have viral loads below 100,000. And they all did at screen, though a number of them had higher viral loads when they actually started the medications. And in general, those ones took a little longer to suppress but you can see that by week 8 everybody was suppressed on this regimen.

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There was one virologic failure at week 36 and that person actually ended up resuppressing despite not having yet switched over to a standard regimen. And then there was one suicide that was felt to be unrelated to the therapy who did have an undetectable viral load before before he died. So, this was what really got the enthusiasm going.

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And then at CROI this year we saw the LAMIDOL study. It sounds like a medicine you take for back pain but it actually is Lami, Lamivudine, and Dol, Dolutegravir. And this was a switch study where people who were suppressed first switched to Dolutegravir plus two nukes. And then if they did well and that they dropped one of the nukes and switched to Dolutegravir 3TC. So, we had 20 patient data before now we have another hundred.

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And in this study pretty much all of them remained suppressed. There was no integrase resistance in the three patients who failed. The SAEs were generally not felt to be related. And so there are now two large phase three studies looking at Dolutegravir plus Lamivudine that will give us an answer. One of the issues is that most of these studies are restricting the upper level of viral load so we may not have data on people with very high viral loads but it'll be really interesting to see the results of this because here's what I predict: the next year at ACTHIV there will be the great debate. It will be three drugs versus two drugs. The three drug approach will be the people who want everybody to be on Bictegravir FTC TAF, saying we know three drugs is great. We've used it for years. FTC TAF are very safe and well-tolerated. Bictegravir has a high barrier to resistance. Why mess with a good thing? And then you'll have the two drug people who will say well why would you use three when you can get away with two. Two looks great. It may be cheaper, we don't know. That's up to the drug company people. And so, I think it'll be a really interesting debate that will keep us keep us entertained for a while. But of course, we've got to see the data first.

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Now don't push this too far. Okay so fortunately in the US we haven't been doing this but all over Europe they've been doing Dolutegravir monotherapy studies. Many of them aren't really trials. They're kind of just like oh we found some people who just happened to be on Dolutegravir monotherapy and we studied them. I don't know how they happened to be on it but they were. And in every single study there were failures with resistance and yet they kept doing it. Every country had to have one. So, I think finally the final nail in the coffin was put at CROI. There were two studies presented. This one actually was a trial where people were either continued on baseline ART or switched to Dolutegravir monotherapy. It looked good at 24 weeks but by 48 weeks it was stopped early because of failure with integrase resistance in three patients.

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And then this was another study that kind of went back and looked retrospectively at people who had done this. And again, nine percent who were switched experienced failure and of that of the 11 patients nine of them had a variety of important integrase mutations. So just because Dolutegravir has a high barrier when it's used in three drug combinations and maybe in two drug combinations, doesn't mean it's perfect. And when you use monotherapy you're stressing it too much. And in fact, we've seen that with boosted PI monotherapy in some of the treatment experienced patient population studies like EARNEST and SECOND-LINE where monotherapy with Lopinavir Ritonavir did cause resistance, which we don't see with two or three drug therapy.

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To conclude, ART continues to improve with respect to efficacy, safety, tolerability, convenience, and barrier to resistance. Investigational drugs and strategies may allow for easier simplification, less frequent dosing, two drug regimens, and potentially lower cost. What's left? Well, I think what's left that I haven't discussed are treatments that do what our ARVs only do up to a point. We want to further decrease residual immune activation and inflammation that you heard about this morning. A vaccine would be nice but we don't seem very close to it yet. Care would be even better. And you heard about that this morning. So, thank you very much for your attention.

[Video End]