Clinical Education Initiative
Support@ceitraining.org

HIV ANTIRETROVIRAL THERAPY 2017: CLINICAL CONTROVERSIES IN WHEN AND WHAT TO START:

Speaker: Raj Gandhi

2/8/2017

HIV Antiretroviral Therapy 2017: Clinical Controversies in When and What to Start
[video transcript]

- [Jim] Welcome to Physician's Research Network. I'm Jim Brown, the course director of the monthly meetings of PRN in New York City. Since our beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management, and prevention of HIV disease, as well as it's coinfections and complications.

00:00:20

We hope this recording of Raj Gandhi's presentation, "HIV Antiretroviral Therapy 2017: Clinical Controversies in When and What to Start" will be helpful to you in your daily practice, and invite you to join us in New York City for our live meetings in the future.

00:00:37

PRN is a not for profit organization dedicated to peer support and education for physicians, nurse practitioners, and physician assistants, and membership is open to all interested clinicians nationwide at our website PRN.org.

00:00:49

And now, allow me to introduce Raj Gandhi, Associate Professor of Medicine at Harvard Medical School, and the Departments of Medicine and Infectious Diseases at Massachusetts General Hospital in Boston.

00:01:01

- Well, thank you all for coming. I'm going to be, and I wanna thank Jim, also, for inviting me back. So, I'm gonna go through in the next 45 minutes or so some controversies in when and what to start in terms of antiretroviral therapy.

00:01:14

And these are the controversies I'm gonna focus on. One is should all HIV-infected patients be treated, including HIV elite controllers? Should HIV-infected patients initiate ART on the day of diagnosis? Should all newly diagnosed HIV-infected patients be started on an integrase inhibitor regimen? Should TAF replace TDF for all patients? How should an ART regimen be chosen in patients with specific comorbidities or conditions? I'll highlight a few. And then, finally, what regimen should you choose for a patient who cannot take abacavir, TDF, or TAF?

00:01:53

Okay, so controversy number one: when should antiretroviral therapy be started? We know from the START study that antiretroviral therapy should be started regardless of CD4 count.

00:02:04

These are well known data. A study of over 4,600 patients who were randomized to either start ART immediately, or to start ART when their CD4 count fell to 350, or when they developed an AIDS-related event. The primary endpoint of the START study was a composite of AIDS-related events, non AIDS-related events, or death. And a little over a year and a half ago, the data safety monitoring board actually recommended not stopping the trial, because the trial continues, they recommended offering ART to all. So, essentially, unblinding the trial. A couple of things I want to highlight in the START study: a young group, median age in this study was 36. At the time the DSMV had all patients start ART, the mean follow-up was three years. The median baseline CD4 count was in the 650s, and the people who deferred ART, the median CD4 count was 408, so it was not very, very low, it was just where they hoped it would be, a little bit above 350. Median HIV RNA was 13,000, so really does not answer the question of elite controllers. Elite controllers are those people who control HIV without antiretroviral therapy. So here the median HIV RNA was about 13,000.

00:03:16

These are the results that were presented a couple years ago. You can see that the overall reduction in either AIDS-related events or non AIDS-related events was substantial, it went down 57 percent. That's on this slide, this part of the slide here. What was interesting is not only did AIDS-related events go down, they actually went down by 72 percent right here in the middle, but non AIDS-related events also went down. Less so than AIDS-related events, but still significantly so. What were the events that went down? Well, TB, kaposi sarcoma, and lymphoma were the three most common AIDS-related events, all of them were less frequent in the immediate group. I find this particularly interesting, cancer rates, if you put together nonAIDS-related cancers and AIDS-related cancers, those are about 60 percent lower in the immediate ART group, so essentially ART prevents cancer in this study. There was no difference, however, in cardiovascular disease rates. A lot of people, like myself, hope that earlier ART might reverse some of the inflammation that leads to cardiovascular disease, but here there was not a decrease in cardiovascular disease. Why might that be? Well, in part it might be the young age group, and remember, they were 36 years of age, and also they were only followed for about three years. It may be that the risk for cardiovascular disease was low enough that they couldn't show a difference. The greatest benefit, interestingly, in terms of overall benefit, was greatest in those who were over age 50, those who had a viral load over 50,000, a low CD4 to CD8 ratio, or a high Framingham risk score.

00:04:49

In the US, we've been recommending HIV therapy regardless of CD4 count since 2012, but in 2015 the evidence was upgraded to an A1 recommendation, basically strong evidence based on randomized clinical trials. But globally, what was really the big impact of the START study and a study called TEMPRANO, which gave similar results, is that WHO adopted a treat all approach for the world, which was a big advance.

00:05:16

But what about the controversy? So, you have a patient who's HIV positive, in this case, I'll give you an example, and I'll ask you to raise your hand, if you would. A 55 year-old man with hypertension and HIV

and diabetes, CD4 count of 500, and an HIV RNA of about 50, and he's been like that for several years, so he's an elite controller, he controls HIV without antiretroviral therapy. How many people would start such a patient on therapy? And how many people would not start such a patient on therapy? Okay, it's interesting. When I give this talk, usually it's more split, here it looks like the preponderance of people wanted to start, but I will say there's not firm evidence either way, so I'll share with you my perspective and some of the kind of rationale for starting therapy. I would agree with most of you, but let's review why we might start.

00:06:05

Here are a couple of reasons not to start ART in an elite controller. There are some drug toxicities, there is a risk of drug resistance if the patient is non-adherent, there is the cost, of course, of the drugs themselves, and there is actually no proof, yet, that ART prevents complications in this very narrow group of people. Remember, elite controllers are only about .3 percent of people with HIV, so it's not a common occurrence, but I think it's an interesting and important patient population.

00:06:31

Here are some reasons to start ART in elite controllers. We know that elite controllers actually, even though their viral loads tend to be below 50, that's the definition of an elite controller, they tend to have higher HIV RNA levels, if you use ultra, ultra-sensitive assays that go down to one copy per mil, they tend to have more immune activation, and they tend to have more inflammation than people who are on ART. So, they are having some viral replication going on. That inflammation and activation may also translate into high rates of non AIDS-related events, for example, they have high rates of subclinical atherosclerosis, if you look at their carotid arteries, they tend to be thicker, that's a biomarker, or a surrogate marker or atherosclerosis. There are some data that elite controllers have higher rates of hospitalization due to cardiovascular disease than ART-treated patients. And there are some people who are sometimes called elite progressors, not a very good term, I don't think, but these are people who essentially have the dwindles in terms of their CD4 count, their CD4 count goes down, their CD4 to CD8 ratio tends to be low. And, there are some limited data, some new data will be presented at CROI suggesting that if you treat elite controllers, you can bring up their CD4 count, you can bring up their CD4 to CD8 ratio, and you can decrease T cell activation. One thing I didn't put on the slide, but one thing people sometimes worry about is if you treat an elite controller with ART and then they stop ART, will they suddenly become a non-controller, will they lose that control because maybe their immune system doesn't see the virus anymore? There are not a lot of data on this, but the data we have is reassuring. That is, the data that we have of people who started ART as elite controllers and then stopped, they don't tend to lose elite control, so that's something you can tuck away in terms of a reassuring part about potentially treating elite controllers.

00:08:23

So, what do I do? I think there's still controversy. I think some elite controllers may really be quiescent. These are the ones who have the highest CD4 counts, they tend to have the lowest HIV RNA, and there are some data from a colleague of mine showing their transcriptional profile-- they might just be different than the more active elite controllers. So, there may be some elite controllers who are really

very quiescent. But I think many elite controllers have a more active phenotype, there is something going on in them. They tend to have decreased CD4 counts, they tend to have elevated CD8 counts, as though their body's trying to fight off the virus, and they can have decreased CD4 to CD8 ratios. So, if you look at your elite controllers, remember, a normal CD4 to CD8 ratio is about one and a half or so, one and a half to two to one. Some of these elite controllers will have ratios of about .5, .6, that's a combination of lowish CD4 counts, and highish CD8 counts. They can have elevated CRPs, again, the inflammation. And sometimes they'll have intermittently detectable virus, those are the more active elite controllers, and those are the people I tend to recommend treatment to. I do admit that we don't have firm data, this is a theoretic rationale, but I think there is some data supporting it, at least theoretic data. Perhaps the one thing, though, that I think all of us should agree on is that elite controllers who don't start ART must be followed carefully. I heard of a case recently from North Carolina of an elite controller who, had not been on ART, and then just fell out of care, and several years later actually, presented with pneumocystis pneumonia, so essentially they had lost elite control. They eventually progressed, and they ended up in the hospital, and I think that patient actually died after being an elite controller. So, if they don't start ART, make sure you monitor them.

00:10:08

Okay, so another case scenario, this is a 29 year-old man. Actually, this is a patient I saw about a month or two ago, he had undergone testing for HIV at a STI clinic, his rapid HIV test was positive, his antigen antibody and confirmatory HIV test were positive, but his RNA was pending, his genotype was pending, his CD4 count was pending, BUN creatinine pending, all labs pending. So, he walked in and the question that our nurse practitioner asked is should we start ART on the same day? So, how many of you would start or are starting ART on such a patient on the same day? Okay, a few of you. How about not yet, you're not starting the same day, you're doing a few more, you know, having them come back? And then how about it depends? Okay, so kind of equal, a little bit more said no, which is certainly the case where I work also, we don't routinely start. But I wanna show you some of the data that's at least kind of supportive of same day initiation. Probably it depends is probably the right answer, it's gonna depend on a whole bunch of things: is the patient ready to start, do you have insurance, does he have insurance, et cetera. But I wanna show you some data that at least supports the idea of earlier and earlier starting.

00:11:20

This is the second controversy: should patients be started on ART on the day of diagnosis? So, why is this even a question? Why are people studying this?

00:11:31

We know that delays in initiating ART may lead to clinical progression, it may lead to disengagement with care. If you tell someone to come back later, maybe it's less urgent to them to get care, and it may lead to sub-optimal outcomes. So, the question that's being asked is does starting ART on the same day improve outcomes? So, there are now three studies that at least, in total, support starting ART very, very early.

00:11:56

One is from San Francisco, which I'll show you. One is from South Africa, and then the last, and this is presented by a colleague of mine, hasn't been published but it was presented about eight or nine months ago, it was from Haiti. So, here are the data from San Francisco, probably the closest, you know, in terms of our own practice. So, this is a study of same-day initiation of ART. This was not a randomized study, the Haiti trial was randomized, this was an observational study.

00:12:21

Eighty-six patients referred to San Francisco General Hospital, recently named Zuckerberg General Hospital, and these were patients who were kind of two unique types of patients. They either had recent HIV, so just in the last six months acquired it, or they had a low CD4 count. This was not all comers, but they got divided into a rapid group, the people who started ART essentially on the same day, and the regimen they usually got was dolutegravir TDF FTC, so a relatively high genetic barrier to resistance, a regimen for which they needed a serum creatinine, but they got that back usually by the next day. And they usually got the first dose in the clinic. The baseline CD4 count in this same day initiation was 474, but look at the range, some people down to a CD4 count of three, other people had a CD4 count of over 1,000. They then compared this in an observational way, again, this was not randomized. Standard of care universal ART, 47 patients, and here people started about three weeks later, that's, I guess, more typical for what many of us have done. Similar kind of baseline CD4 count. Here, the outcome was time to virologic suppression, and you can see in the rapid group, not surprisingly, they started ART 21 days earlier, they had viral load suppression much quicker than the standard of care universal ART group. The median time from referral to viral suppression was only 1.8 months in the rapid group, and it was a little over four months in the standard group. So, you could see a significant difference between those. Now, this was not a clinical health outcomes study, this was just virologic suppression, but since viral suppression translates into less infectivity, this seems to also be beneficial in terms of the public health, and it seems plausible that this would be of benefit, even clinically, although they couldn't show that here.

00:14:09

Another study, this is a study in Haiti, so a totally different healthcare setting. ART-naive adults, CD4 count less than 500, no TB. Here they were randomized to a standard group, I won't go through all the details, but in the standard group, ART was initiated at day 21, and then they had physician/social work visits before and after. And in the same day group, those patients were randomized to start ART on the day of diagnosis, and then they had physician and social work visits. And this study actually got stopped early, and it got stopped early because of better outcomes in the same day group. And what was interesting is the outcomes were some pretty hard outcomes in terms of clinical benefit.

00:14:50

Initiated ART: 100 percent in the same day group, 90 percent or so in the standard group. Alive and in care at one year: 80 percent in the same day group, 71 percent in the standard group. In care with a viral load suppressed at less than 50: 54 percent in the same day group, 42 percent in the standard group. And perhaps most surprisingly, death: 7 percent in the standard group, lower, significantly lower, in the

same day group. Now, obviously the circumstances in Haiti are very different than they are here. Serena Kurnic, who presented these data, presented at one of our conferences recently, and the alive and care of virologic suppressed are not what we would hope for, we hope for 80, 90 percent of people virologically suppressed in care, or higher. And some of this was kind of movements within Haiti. But still, this, in one of the hardest places in the world to work, showed a benefit to same day initiation, and I think what I take away from this is my usual hesitancy to start until everything is kind of all perfect, that just the empowering act of starting ART, this is a serious illness, we're going to treat it, we're going to allow you to take back control, really can bring people into care and keep them into care. And so I'm starting earlier than I used to, I haven't started, that same patient I told you, we didn't start the same day, but we started within a few days after that, after we had a few other things back and his insurance sorted out. And so, I think these data are pushing us to earlier and earlier start, and in the question and answer, I would be happy to see what peoples' thoughts are, and peoples' experience.

00:16:27

Okay, so controversy number three: should all newly diagnosed HIV patients for their initial regimen be started on an integrase inhibitor?

00:16:37

Just as a reminder, these are the classes of HIV medicines: RT inhibitors act on reverse transcriptase, these are nucleoside RT inhibitors like tenofovir, abacavir, 3TC, and FTC. Nonnucleoside RT inhibitors like efavirenz and rilpivirine. Once HIV gets into the cell, it reverse transcribes itself at that level of the virus, and then the DNA gets integrated into the host genome. That's where integrase inhibitors work, dolutegravir, raltegravir, elvitegravir, cobi. The integrated DNA then gets transcribed and translated into proteins, and those proteins get cleaved by HIV protease, and the protease inhibitors prevent that cleavage. And if the virus can't cleave the poly proteins, then it can't form a mature virus, so that's where protease inhibitors work.

00:17:24

We have over 25 options, actually, I think there's over 27 options, including six different single pill regimens, one pill once a day regimens. So, how does one go about choosing between those 27 different options?

00:17:40

Here are the latest guidelines from the International Antiviral Society USA, IS USA. They've boiled it down to essentially four recommended initial regimens, and you'll notice all four of them are integrase inhibitor regimens. Dolutegravir, abacavir, 3TC, a single pill combination. Dolutegravir plus TAF FTC. Elvitegravir, cobi, TAF FTC, and raltegravir, TAF FTC, so basically four integrase inhibitor regimens, and you'll see that TDF, tenofovir disoproxil fumarate, has fallen off of the list of the IS USA guidelines. Although, they do qualify this, and this may not get as much publicity, but they say if TAF is not available, TDF remains an effective and generally well-tolerated option. And, they also make the observation that some clinicians may prefer to continue using TDF until we have broader experience with TAF in clinical practice.

00:18:33

The other major guideline in the US of course is the DHHS guidelines. Essentially the same four options in terms of integrase inhibitors, but here TAF and TDF are both retained, and the DHHS guidelines also include one protease inhibitor-based regimen, and that's boosted darunavir plus TDF FTC, or TAF FTC.

00:18:57

I do think that there are now randomized trials indicating the integrase inhibitor-based regimens really are optimal for most patients with newly diagnosed HIV. I'm gonna mention some of those trials, and then I'll just give you a couple of scenarios where I might not use an integrase inhibitor. But, I do think for the vast majority of patients, an integrase inhibitor-based regimen is optimal.

00:19:17

Here was the first time that efavirenz was ever beat in a clinical trial. So, this is a head to head trial of dolutegravir plus abacavir 3TC versus an NNRTI, efavirenz TDF FTC. And in the single study, you can see that a higher proportion of patients had a suppressed viral load at 48 weeks, and it actually went out even further if they got dolutegravir than if they got the NNRTI. Some of this was driven not by virologic superiority, but by better tolerability, there were more discontinuations in the efavirenz group, but nevertheless, superiority to the dolutegravir, to the integrase inhibitor group.

00:19:59

How about integrase inhibitors versus protease inhibitors? There's now several trials supporting using integrase inhibitors over protease inhibitors. ACTG5257 compared raltegravir to boosted adazanavir, or boosted dorunavir, and raltegravir was superior. Again, largely based on tolerability. Dolutegravir has been compared to boosted darunavir in the flamingo study, again dolutegravir is superior. In women, there's been two large trials in women, one is called WAVES and one is called ARIA. Elvitegravir cobi was superior to boosted atazanavir in women. And then, the most recent, and this hasn't been published as far as I know, but was presented about six or eight months ago in South Africa, dolutegravir abacavir 3TC is superior to boosted atazanavir plus TDF FTC again in women. And you can see about a 10 percent difference favoring the integrase inhibitor arm.

00:20:58

Which integrase inhibitor should you use? There's actually precious little head-to-head comparison of different integrase inhibitors. Elvitegravir versus raltegravir has been compared head-to-head only in treatment-experienced patients, and both drugs were essentially comparable. Dolutegravir has been competed head-to-head against raltegravir in the SPRING-2 study, which is a treatment naive study, pretty much a tie. Raltegravir and dolutegravir were comparable. But in treatment-experienced patients in the SAILING study, dolutegravir was actually superior to raltegravir.

00:21:32

What are some pros and cons, how do you choose between the integrase inhibitors? So, here are some of the pros and cons of the different drugs. Raltegravir, still the longest track record, this goes back almost a decade, and it's the cleanest when it comes to drug interactions. This one has the fewest drug

interactions. Some of the cons, we know this, twice daily, dosing of raltegravir is still indicated. I'm gonna show you some data supporting once daily dosing of a new formulation of raltegravir in a study called ONCEMRK, we'll talk about that in a minute. Right now, though, a con is that it's twice a day, that may change. And, raltegravir is not coformulated as part of a single pill regimen. What are the pros of elvitegravir cobi? It is actually available in a single pill combination with TDF FTC and with TAF FTC, but some of the cons, it does have the most drug interactions because cobicistat which inhibits CYP3A4, there is a food requirement as well. Some of the pros of dolutegravir, it's available in a single pill regimen with abacavir 3TC, and it does have a high genetic barrier to resistance. With accumulating data, it seems to me, at least, that this integrase inhibitor is the most forgiving in terms of having the most difficulty for resistance to develop. Some of the cons, it's not coformulated with tenofovir, so if you want a single pill combination, it has to be given with abacavir. It does have the largest pill size of the single pill regimens, and there is a drug interaction between dolutegravir and metformin.

00:22:59

This is the ONCEMRK study, this is presented this past July. A little over 800 patients, randomized to either get a new formulation of raltegravir, it was two pills that added up to 1,200 milligrams, once a day, plus TDF FTC, and that was competed against standard raltegravir, 400 milligrams BID, plus TDF FTC. You can see essentially no daylight between the two curves. Viral load suppression exactly the same between this new formulation and standard raltegravir, so non-inferior. And there are reasons to think that this once a day raltegravir, which will be two pills, but once a day, may be available this calendar year. We'll see, this is still being reviewed by the FDA.

00:23:46

What are some limitations of the integrase inhibitors? Again, I will say at the outset that most of my patients, I do give integrase inhibitors to, but some of their limitations: Remember that cations do affect integrase inhibitor absorption, so the other classes of HIV drugs, NNRTIs, PIs, those don't get affected by magnesium, calcium, aluminum, but integrase inhibitors do, so you have to remember to tell your patients to stagger the dosing. There are some idiosyncratic adverse events, rhabdomyolysis can occur with raltegravir. I don't know how many of you have seen this in your clinical practice, I'll ask you at the end, but there are some reports from Europe, predominantly of insomnia, anxiety, depression, with dolutegravir. These are case series and cohort studies which are uncontrolled, and in one study it was as high as 15 percent. There is a publication that's coming out soon looking at the US experience in clinical trials, as well as a US-based observational cohort that's not seeing this signal with dolutegravir, but something that is being at least discussed. And then, one other limitation of integrase inhibitors, the only integrase inhibitor single pill regimen that contains tenofovir right now is with elvitegravir cobi, and then I already mentioned elvitegravir cobi has drug interactions. There is a new unboosted integrase inhibitor called bictegravir. This integrase inhibitor does not have a booster, and it's being developed for use with TAF FTC, and at CROI next week there's going to be a presentation on a randomized trial comparing bictegravir to another integrase inhibitor, so we'll see the results of that next week. So, that may be an option for an unboosted integrase inhibitor with a tenofovir-containing kind of backbone.

00:25:36

When do I not use integrase inhibitors? One scenario where you might not use an integrase inhibitor is in a patient who has very uncertain adherence, or in someone you need to start on ART before you can get the resistance test result back. Someone, say, with an opportunistic infection, or acute HIV, you don't wanna wait two or three weeks, or even one or two weeks to get the resistance test back, you wanna start ART soon. Here the DHHS guidelines still recommend that you consider using a boosted PI, boosted darunavir, and it's really because of the high genetic barrier to resistance. It is really hard for the virus to get resistant to a boosted PI. The DHHS guidelines do mention, though, that dolutegravir might also be used in this setting because of that high genetic barrier to resistance, but this is one scenario where I'll sometimes look for a protease inhibitor. Another setting, this is like almost the opposite, someone who has a very low HIV RNA, and a high CD4 count, sometimes I'll consider using an NNRTI, rilpivirine, either with TDF FTC or with TAF FTC. This is a very small pill, it's also well-tolerated. And in the study in people whose viral load was less than 100,000, it was actually superior to efavirenz TDF FTC if the viral load was less than 100,000. Remember, you can't use rilpivirine if the CD4 count is low, or if the viral load is over 100,000, but if that's not the case, it's something you might consider. And also remember that rilpivirine has a really strict food requirement, you have to give it with at least 390 calories of food, so they can't take it on an empty stomach. You have to avoid a PPI, and you have to stagger H2 blockers, they need acid for rilpivirine.

00:27:16

And then the last scenario where I sometimes don't use an integrase inhibitor, or at least I think about it, is in a person with TB on rifampin. Remember, rifampin interacts with a variety of drugs, including protease inhibitors. There are the most data worldwide, by far, with using efavirenz TDF FTC if you have someone on rifampin. And that's in part because rifampin has less effects on efavirenz concentrations than other ARVs. Those of you who've been doing this for a while will remember we used to dose adjust efavirenz up to 800 milligrams a day when we gave rifampin, but there are good data now saying you don't really need to do that, you can keep efavirenz at standard dosing, 600 milligrams a day. You sometimes will use dolutegravir or raltegravir, don't use elvitegravir cobi, 'cause the cobi will interact with the rifampin. But if you use raltegravir or dolutegravir, you have to increase the doses. I think sometimes I'll use an integrase inhibitor, sometimes I'll use efavirenz in the setting of someone on rifampin.

00:28:12

Okay, so controversy number four: should TAF replace TDF for all patients? So, TAF, I think, is probably well known to most of you.

00:28:22

This is a pro drug of tenofovir that concentrates in cells and then gets converted to the active drug tenofovir. Because TAF concentrates in cells, you give less of it, and so there's 90 percent lower plasma tenofovir levels as compared to TDF, tenofovir disoproxil fumarate, the tenofovir you've all used for many years. So, in a large clinical trial that I'll show you the results on, and which were updated just a few months ago, elvitegravir cobi FTC TAF was competed head to head against the same drugs, so

elvitegravir cobi FTC TDF, so it was basically TAF versus TDF for initial therapy in about 1,700 patients, randomized.

00:29:03

And this showed, on this graph here, essentially virologically, TAF worked as well as TDF, really no difference. But there were some potential toxicity benefits of TAF, it was associated with a smaller decrease in estimated GFR than was TDF. You can see here the magnitude. There was less proteinuria with TAF than with TDF, there was a smaller decrease in bone mineral density, TDF causes bone mineral density decline, and there was less of that with the TAF. There was a greater increase in cholesterol, LDL, HDL, and triglycerides, all of them were a little bit higher in the TAF group than in the TDF group. Why might that be? Well, it turns out the tenofovir itself lowers cholesterol, so if you have less tenofovir around, you actually get a higher cholesterol. We know that tenofovir lowers cholesterol, 'cause if you change someone from, say, abacavir or, in the old days, ACT to tenofovir, their cholesterol tends to go down. So, if you give them TAF, they have a higher cholesterol, but interestingly the total cholesterol to HDL ratio was the same. So, all of the types of cholesterol are lower with TDF than with TAF. And then, the final point to make about TAF is it is FDA approved for down to a lower eGFR. I get nervous with TDF once the eGFR gets below about 50 to 60. This is approved for creatinine clearance down to 30, that is, TAF is.

00:30:30

New results came out with that same trial that I just showed you, these are 144 week results, so what is that? Two years? So, a couple of years of results. This showed that TAF was superior to TDF at 144 weeks, so this is the virologic suppression, so once you get out a little further, superior results with TAF, and there were more renal events leading to discontinuation in the TDF group, 12 versus zero. This was presented this past September. In addition to initial therapy studies, there's been a whole bunch of these switch studies, so the elvitegravir cobi studies that I just showed you were initial therapy, treatment naive, but there's a bunch of studies where people already virologically suppressed either stay on TDF FTC, or they switch over to TAF FTC.

00:31:18

One study involved switching from TDF FTC to TAF FTC, and kept the third drug going over 600 patients. There was a study basically switching from rilpivirine TDF FTC to rilpivirine TAF FTC, a little over 600 patients. And then finally, a study of essentially changing from efavirenz TDF FTC to rilpivirine TAF FTC, over 800 patients. Every single one of these studies essentially had the same result, which is why I put them on the same slide. When you switch, you maintain virologic suppression, you improve eGFR and proteinuria, you improve bone mineral density, and then you have that increase lipids but stable total cholesterol to HDL.

00:32:00

These are the things we have right now. We have elvitegravir cobi FTC TAF that was approved in November of 2015 based on initial therapy studies and switch studies. We have rilpivirine FTC TAF that was approved just under a year ago. That's approved basically based on bioequivalence in switch

studies. And then we have FTC TAF approved also a little under a year ago based on switch studies. There is a phase three clinical trial of the first protease inhibitor, single pill combination with TAF, which is called cobicistat-boosted darunavir with FTC TAF, and this is in phase three clinical trials, and we'll see the results, I think, soon.

00:32:42

Okay, so should TAF replace TDF for all patients? So, I've already mentioned some of the reasons to choose TAF. TAF is virologically as effective as is TDF. And, I've shown you that compared with TDF, TAF has more favorable effects on renal and bone markers, and I think this is particularly important if you have a patient who already has renal or bone disease, or in someone who's at high risk for renal or bone disease. And the last reason to choose TAF might be that the cost of TAF and TDF regimens currently are fairly comparable. The reasons to continue to use TDF: compared with TAF, there are more and longer term data with TDF, particularly if you look at treatment-naive patients. There are more favorable effects on cholesterol, although the total cholesterol to HDL doesn't change. The renal and bone marker advantages of TAF are not yet known to translate into better clinical outcomes. And I think this last point is, perhaps, the most important: that TDF regimens are likely to become cheaper than TAF when TDF goes generic. TDF is supposed to go generic sometime this calendar year, 2017, and so people anticipate, at least, that the TDF regimens may be cheaper.

00:33:52

One of my colleagues at Mass General, Rochelle Walensky, did this cost effectiveness analysis, and she just asked the question: how much more should society be willing to pay for TAF over TDF, because of those improved toxicities? She modeled all of those renal and bone effects, and when she did cost effectiveness-- this is not cost savings, cost effectiveness-- they said that basically those benefits of TAF should justify a price increase of TAF of about 1,000 dollars a year over TDF. Right now, they're comparable price. So, once generic TDF 3TC becomes accessible at lower costs, she and her coauthors urged the company to basically decrease the price of TAF to make it still a little bit more than TDF, there are benefits to it, but not substantially more than TDF. So, we'll see if that happens.

00:34:43

When should you definitely use TAF over TDF? In patients with osteoporosis or osteopenia, I think I would, it's unequivocal, I would absolutely use TAF. Patients with renal disease, or evidence for proximal tubular dysfunction, for example, proteinuria, I would definitely use TAF. And I will say, this is certainly a growing proportion of my patients, the graying of the epidemic, the median age in my clinic is 54, so there's no doubt that many of my patients fit into this group. When should you definitely not use TAF? One scenario where you do not wanna use TAF is in a person on a rifamycin. Right now, if you look at the label for TAF, they caution against using TAF with people on rifampin, rifabutin, because you might get decreased TAF levels. This actually came up with one of my colleagues recently who had an injection drug user who had a bone and joint infection, needed rifampin to combine with his anti staph drug in his bone and joint infections, and also had HIV, and so in that setting, they couldn't use TAF because the patient was on rifampin, or rifabutin, I think, was one of the options, but was on rifampin. So, in that very specific scenario, remember not to use TAF in someone on a rifamycin. Right now, it's not indicated

for pregnant women, and then it's not yet indicated for PrEP. There is a large clinical trial going on comparing TAF to TDF, TDF FTC versus TAF FTC for PrEP, but right now I would not use TAF for PrEP, I would use TDF FTC.

00:36:12

Okay, so controversy number five: how should you choose an ART regimen in patients with specific conditions?

00:36:18

Here are some, again, the pros and cons of our choices, so abacavir 3TC is not nephrotoxic, that's a pro, and it's available in a single pill regimen with dolutegravir, which is an unboosted, once a day, integrase inhibitor. Some of the cons: you must confirm the patient is HLA-B5701 negative, and some studies but not all have shown an association between abacavir and cardiac events. TDF FTC, it's available with several single pill regimens, with efavirenz, with rilpivirine, with elvitegravir cobi. It results in lower lipids, and it's active against hepatitis B, those are all advantages. Some of the cons: it does have greater nephrotoxicity than abacavir and TAF, and as I'll show you in a moment, there are greater declines in bone mineral density with TDF than with abacavir or with TAF. I've gone through some of the pros of TAF already: its more favorable effects on renal and bone markers, it's available as a single pill combination with elvitegravir cobi and rilpivirine. And there are data, I don't show this in this presentation, but there are data showing that TAF is effective against hepatitis B. In a HIV context, if you switch people from TDF to TAF, they maintain hepatitis B control. And in hepatitis B mono infection, not HIV co-infected, there was a head to head randomized control phase three trial of TAF versus TDF, where essentially TAF came out just as good as TDF for hepatitis B, with the same benefits on renal and bone markers. In fact, many of you may know that TAF as just a standalone drug was recently FDA approved for hepatitis B mono infection, just about a month or two ago. Some of the cons: there are less long term data as I mentioned, particularly for initial therapy.

00:37:59

How do I customize ART? So, in a person who's, I would say, an estimated GFR of less than 60, I then tend to use abacavir plus 3TC. If the eGFR is less than 50, then I dose reduce the 3TC, or I'll use TAF FTC as a single pill if the creatinine clearance is less than 30. Remember, it's not all about the nucleosides, there are data showing that boosted atazanavir and boosted lopinavir, which is less commonly used, are also associated with kidney disease. In a person with high cardiac disease, I tend to favor TDF over TAF because of the uncertainties around abacavir and cardiovascular disease. In a person with hepatitis B, I think either TDF FTC or TAF FTC are fine. In pregnancy, it's now recommended, actually ACT finally got demoted out of the pregnancy recommendation, so it's now abacavir 3TC or TDF FTC plus raltegravir among the integrase inhibitors, and among the boosted PIs, boosted atazanavir or darunavir. And then I'll show you for osteoporosis, clearly I would avoid TDF.

00:39:01

Here are the data showing that when you start ART, essentially, regardless of regimen, you will lose some bone mineral density, so in both of these graphs you're seeing a decrease in the bone mineral

density as a function of time over the first two years. You'll see bone mineral density stabilizes after the first year, but it stabilizes at a lower level in someone given TDF than in someone given abacavir. All regimens produce bone mineral density, but TDF more than abacavir. And, similarly, when you start TAF, here in the purple versus TDF, stabilizes but at a better level with TAF than with TDF.

00:39:38

This study has really impressed me. This is a switch study, and what you can see if people stay on their TDF, their bone mineral density doesn't change much, but the bone mineral density actually goes up substantially, a little over one and a half percent, if you switch from TDF to TAF. What that means to me is that the TDF, the tenofovir, is suppressing the bone mineral density, and when you release that pressure, then the bone mineral density recovers. So, switching to TAF significantly improves spine and hip BMD, decreases PTH, and decreases serum bone markers.

00:40:14

Which regimen should you use in a patient with osteopenia or osteoporosis? I would avoid TDF, I'd use abacavir or TAF instead. Which is better, abacavir or TAF in terms of the bone? We don't know. I understand Todd Brown spoke recently, we'll have to ask him what he thinks, but there's no comparative data yet that really answers the question of TAF versus abacavir head to head. But, there is a randomized trial that's comparing abacavir 3TC dolutegravir, to TAF FTC bictegravir, that's that unboosted integrase inhibitor. That may allow us to tease out which of those is better on the bone, abacavir or TAF.

00:40:51

The final consideration when I'm trying to customize ART is drug-drug interactions. In someone in whom I'm anticipating hep C treatment, I tend to use raltegravir or dolutegravir because they're cleaner when it comes to drug-drug interactions. In someone on acid-lowering therapy, I either avoid altogether or am incredibly cautious with rilpivirine or atazanavir. Both of those need acid to be absorbed. Cations, any kind of multivalent cations, so, you know, calcium, magnesium, aluminum, most of those require staggering dosing of integrase inhibitors. And then CYP3A4 metabolized medications, I either avoid or am very cautious with PIs or cobicistat, 'cause those inhibit CYP3A. A really useful website if you don't use it already is this website at the bottom. You can remember it if you just put in Liverpool and HIV, and this is the University of Liverpool website, an excellent website when it comes to drug-drug interactions. I use it almost every time I start someone who's on polypharmacy on a new HIV med. One interaction I really wanna highlight, because it's a particularly common one is with exogenous steroids. So, because so many patients get exogenous steroids, either inhaled steroids for their asthma or for their allergic rhinitis, more and more as people age, they're getting injections of steroids, I wanna highlight this one in particular. Injectable steroids, if you get a patient who has a trigger finger, or more commonly a back injection of an epidural steroid injection, remember that those levels of the steroids are increased substantially by either PIs or cobicistat.

00:42:25

We did a study at MGH where basically we looked at all of our patients retrospectively who are on PIs and who got a steroid injection, and 10 percent of them got clinical evidence, not subclinical but clinical evidence either of Cushing syndrome, or adrenal insufficiency, so really a very substantial number. They usually inject triamcinolone, and that will accumulate, so I've taken to switching people off of PIs and cobi if I know they're gonna get an injection. The other one to really highlight is inhaled steroids, I think fluticasone is now available over the counter, so something to caution your patients about. Budesonide another inhaled steroid, these are somewhat lipophilic, long-lasting inhaled steroids, so their levels are also increased by PIs and cobicistat, and so I'd caution people not to use either of those. If they have to use an inhaled steroid, and many people do, beclomethasone has been studied in people on PIs, and that seems to be safe, so that's actually the only one I remember, and the only one I use is beclomethasone.

00:43:27

Okay, and then the last controversy, and then we'll open it up for comments and questions. So, what do you do in a patient who you can't use TAF, you can't use TDF, and you can't use abacavir?

00:43:37

Here's an example of this type of patient, someone who's got HIV, diabetes, hypertension, and chronic renal insufficiency. This person has a creatinine clearance of less than 30, so too low to use TAF. Has an HIV RNA of 30,000, and a CD4 count of 450, that'll become important in just a minute, so not a very high viral load, not a very low CD4 count. And, is B5701 positive, so you can't use abacavir.

00:44:05

This is my last question for you: which of these regimens has the most evidence, I guess, behind it? So, would you use in this person boosted darunavir plus TAF FTC? No, okay, good, 'cause the creatinine clearance is too low. Boosted darunavir plus raltegavir? No, okay, only a few. Dolutegravir plus 3TC? Okay, this is a tough one, yes. Dolutegravir plus rilpivirine? Okay, so this is a tough one, I think those last three, especially two and four, got a few votes, not everyone voted. Okay, so this is the last section, so what do we know about regimens that either do away with nukes, nucleosides, altogether, or limit them?

00:44:57

For initial therapy, there are a couple of options, and they're all on this slide, really. The so-called GARDEL regimen, boosted lopinavir plus 3TC, was studied, randomized trial, it's non-inferior to two nukes plus boosted lopinavir. But I don't use it, and I don't think most of you would use it, also because there's just too many pills, there's just too much side effects of boosted lopinavir, especially GI side effects. But this does work, it just has too many side effects, too much pill burden. Boosted darunavir plus raltegravir a few of you liked, there was a randomized study called NEAT001 that looked at this nuke-sparing regimen, no nukes at all, and found it to be non-inferior, so just as good as boosted darunavir plus TDF FTC. Why don't more of us use it? At the extremes, it did not work as well, so if the CD4 count was less than 200, or if the viral load was over 100,000, it didn't seem to be strong enough.

Basically, there were more failures with the nuke-sparing regimen when the CD4 count was less than 200, or when the viral load was over 100,000. It just wasn't potent enough at those extremes. A regimen to keep your eye on is the dolutegravir 3TC regimen, this is being studied. So, this is a nuke-light, I guess, there's a nuke there but it's not abacavir, it's not TAF, it's not TDF. There was a 20-person study called PADDLE that looked very good. Patients suppressed when they got dolutegravir 3TC, but it was only 20 patients, but it looked good. And then about a little over 100 patients are in a single arm study called ACTG5353, a single arm study looking at dolutegravir 3TC. That hasn't been reported yet, but will be soon. This last summer, the GEMINI trials started. These are two big phase three randomized clinical trials comparing dolutegravir 3TC versus dolutegravir plus TDF FTC. So, a nuke-light versus a standard regimen, and they were launched in the summer of 2016, and that, I think, will be the definitive answer as to whether dolutegravir 3TC is as good as two nukes and dolutegravir. You've got many more options if you've gotta switch off of two nukes and a third drug. There are many good options in terms of someone who you got suppressed, and now you need to switch them maybe because of toxicity.

00:47:18

In the OLE study, boosted lopinavir plus 3TC or FTC looked fine once they were suppressed, looked just as good as continuing two nukes plus the boosted lopinavir. In the SALT study, boosted atazanavir plus 3TC looked fine. And then in the small study, boosted darunavir plus rilpivirine looked fine. Here's a whole bunch of studies to keep your eyes on: boosted darunavir plus 3TC, boosted darunavir plus dolutegravir, these are switch studies that are coming down the pike. This study, I have a patient on right now, dolutegravir plus 3TC once they were suppressed, and this one I wanna highlight, because about a month ago there was a press release on this, and you're gonna see data at CROI for someone suppressed already, can you switch them to a totally nuke-sparing regimen of dolutegravir rilpivirine? I'll show you in a moment. And then, I don't have time to talk about this one, but there's also a long-acting intramuscular cabotegravir plus rilpivirine with the very appealing name of LATTE-2, not like a latte, that's being studied.

00:48:19

For those of you who may not have seen this press release, we haven't seen the data, but you will next week, I think it's on next Tuesday they're gonna present these data. These are phase three clinical trials of switching patients who are already suppressed from a three or four-drug regimen to a two-drug regimen with no nukes, dolutegravir plus rilpivirine. The primary endpoint was patients less than viral load of 50 at 48 weeks, and the press release said that the two-drug arm was non-inferior, met the primary endpoint of non-inferiority. And regulatory submissions they said in the same press release of dolutegravir rilpivirine as a single tablet regimen are being planned for this calendar year, so stay tuned. I think when Tim Wilkins presents the CROI update in March, I'm sure he's gonna mention the SWORD studies.

00:49:06

Okay, so let me conclude: should all HIV-infected patients be treated? I think clearly yes, and I think you can make a case for treating elite controllers, even though there's not proof of that, but I think you could make a case for it, and you could make a case for initiating ART sooner and sooner, even on the

same day of diagnosis. Should all HIV-infected patients be started on an integrase inhibitor regimen? I think most clearly should receive an integrase inhibitor. There may be a few scenarios, and I've tried to outline a couple of where you might wanna choose a different regimen, but most people I'd use an integrase inhibitor. Should TAF replace TDF for all patients? I think for patients with bone and renal disease, TAF is particularly advantageous, and then people who are at risk for those as they age, I think it's got advantages. How should ART be chosen in patients with comorbidities? Clearly, I would customize based on effects on bone, kidney, cardiovascular disease, viral hepatitis, and then the drug interactions. And then last, what regimen should be used in patients who cannot take TAF, TDF, or abacavir? Right now, the nuke limiting regimens are limited, but there are many new options that are being studied. So, with that I'm gonna stop. Thank you for your attention.

[Video End]