



Clinical Education Initiative
Support@ceitraining.org

UPDATE ON IAS PARIS: FOCUS ON ART

Speaker: Roy Gulick, MD, MPH

2/8/2017

Update on IAS Paris: Focus on ART
[video transcript]

[00:00:01]

Welcome to Physicians' Research Network. I'm Jim Braun, 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 its co-infections and complications.

[00:00:20]

We hope this recording of Trip Gulick's presentation Update on the International AIDS Society Conference in Durban: Focus on Antiretroviral Therapy 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.

[00:00:36]

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. And now, allow me to introduce Trip Gulick, Rochelle Belfer Professor in Medicine and Chief of the Division of Infectious Diseases at Weill Cornell Medicine in New York City.

[00:01:00]

Okay, great. Good evening, everybody. How many of you went to Durban? Raise your hand. Okay, a couple. You can go but everyone else stay. I have no disclosures, by the way. One of the things about having the International AIDS Meeting is that we pause and take stock of where we are so this was an opportunity to do that in Durban.

[00:01:25]

So, where are we with HIV? Current estimates 17 million people are on ART worldwide. That's almost half of those who need it. However, 20 million people are still not on antiretroviral therapy. They estimate 8.5 million lives have been saved since 2000 with ART. Last year, 2 million new people went on ART but 2.1 million people were newly infected with HIV globally. And worldwide, only about a third of people are virologically suppressed. Since 2003, AIDS-related deaths have decreased 43 percent. And that's almost certainly all due to ART. The life expectancy of a 20 year-old with HIV infection who's appropriately treated today is an additional 55 years, so living into his or her mid 70s. 85 countries Carmen, they said at Durban, have now eliminated mother to child transmission. She mentioned Cuba or perhaps Puerto Rico is number one. But now 85 countries, which is remarkable. Eight countries approved PrEP in July but something big happened that month and that is the EU just approved PrEP for all 28 member countries as well. As you know, a grand total of one patient has been cured and only one vaccine study has ever showed efficacy of about 30 percent.

[00:03:09]

What was the IAS 2016 Durban meeting like? Well, we did go back to Durban and if you'll remember, the meeting was in Durban 16 years ago, in 2000. It was the first time that the IAS meeting had actually gone to the developing world and the first time that it had been in Africa. So, this was a big thing to come back to Durban. You'll also remember that in 2000, we had triple combination therapy along with our colleagues in developed countries, but mid and lower income countries still were treating with one or two drugs. So, there was a tremendous imbalance at that meeting and politically that meeting was what got everything going to bring ART to the developing world. So, it's really a tribute to go back there.

[00:03:56]

There were over 15000 people who attended, representing 153 countries, and there were over 2,300 abstracts and I'm going to cover them all. Right before the meeting, the UNIDS updated their epi data and I just picked out a couple of slides that I thought were interesting. This is the number of people living with HIV on ART from 2010 to 2015.

[00:04:25]

So, notice the huge increase even just over the past six years going from seven and a half million in 2010 to 17 million people as of the end of 2015, an enormous increase.

[00:04:41]

This shows you two things. So, one is the percent of people with HIV who are covered with ART. You go back to 2000 and you can see it's a very small number of people. But you go to 2015 and this translates to about, as I said, 46 percent of people now covered with ART who are HIV infected, almost half. And then the other line that's of equal importance here is the death rate from AIDS. You can see that that peaked in about 2004, 2005 and as I mentioned, is now down a significant amount since its peak, almost certainly related to the increase in ART.

[00:05:23]

These are new infections by region of the world. You can see from the back of the room most of the over, the last six years, mostly new infections are sort of flat but there's one area of the world that's showing a tremendous increase that you should note and that's Eastern Europe. So, they're seeing a tremendous increase there. It's multifactorial. Most of the spread there is injection drug use and these countries are not particularly interested in trying to stop the spread of HIV.

[00:05:55]

Here are the new infections globally in 2015 broken down by age and gender and you can see the number of young people who are acquiring HIV. So, if you look at men, 14 percent are under the age of 24 and if you look at women, 20 percent are under the age of 24. So, increasingly HIV worldwide is an infection of young people and women are more affected than men at younger ages. Some more stats just because it's interesting.

[00:06:33]

Pediatric HIV has decreased 60 percent in recent years. However, adolescent HIV has decreased only 8 percent and in fact, if you look globally, HIV is the number two cause of deaths in adolescents globally. That was pretty stunning. Seventy percent of pregnant women are now on lifelong ART by the end of 2015, an enormous accomplishment. As I mentioned, ART went from about seven hundred thousand people in the year 2000, when the conference was in Durban the first time, to currently 17 million. Can't talk about HIV without politics. 77 countries on the globe criminalize homosexuality. A couple of regional statistics. I already alluded to the fact that the big growth area for HIV is Eastern Europe and Central Asia. HIV is up 57 percent over the last six years. And of course we know how to prevent it, so that's a particularly sobering statistic. Only 20 percent of people in the region who are HIV infected are on ART. And then we don't have to look farther to our own data to show in the US, an increase of 27 percent in HIV infections in young men between the ages of 25 and 34. So, we still have our work to do right here. Again, the conference was in Africa. There was a focus on statistics from Africa.

[00:08:03]

As you know, Sub-Saharan Africa accounts for 70 percent of the world's HIV infections. However, since 2000, new HIV infections in sub-Saharan Africa are down 41 percent. That's stunning. And deaths are down 34 percent. So, great gains in this area of the world. I alluded to this before. Young women under the age of 34 are eight times higher rate of HIV than young men of the same age. And then South Africa was our host country. South Africa has 3.4 million people on ART. That's the number one country globally in terms of people being treated for HIV. Mother to child transmission in South Africa has now been reduced to 4 percent. HIV in children has dropped 76 percent since the year 2009 and 50 percent of Durban sex workers are HIV-positive. So, a bunch of statistics but give us an idea of what's going on in the world in terms of HIV at this point in time. Now I'd like to review conference data for you. I've divided it into some of the questions we've been considering for a long time.

[00:09:21]

ART: When to start? We think we know the answer, right? Now or whenever the patient's ready. There was some new data from the START study, which was the definitive study that really showed us that we should be treating all people and you're well aware of those results.

[00:09:38]

But this was a new sub analysis.

[00:09:40]

Just to remind you, START took people who were very healthy. They were ART naïve, CD4s over 500, and they were randomized to two strategies: start ART right away or wait until either the CD4 dropped to 350 or they had a clinical AIDS diagnosis. The primary endpoints were serious AIDS, serious non-AIDS conditions like cardiovascular disease, renal, liver, and non-AIDS cancers. And then all cause death was looked at. And you know the overall results of course showed that there was a significant benefit to starting early in terms of all the clinical endpoints. But what they did with this new presentation was to go back and look at factors and see were their particular subpopulations who benefited more in terms of reducing clinical events by starting earlier? The first one they looked at was age.

[00:10:34]

What you're looking at here, and it will be the same for all the figures I show, in red is the immediate group and in blue is the deferred group and we're looking at clinical events. So, the group that pops out again, the biggest separation from the back of the room looks like age over 50. There were significantly more clinical events in the group that waited to start than those who started earlier. And if you scan those three, it looks like it's much more pronounced in that group. Similarly, they looked at CD4:CD8 ratio. They tested a number of factors but the ones I'm going to show you were the ones that jumped out. Those who had a ratio less than 0.5, again you see a profound separation in the lines favoring immediate initiation. HIV RNA. You might guess that that would be an important factor. For those who had viral load levels above 50,000 again, you see a big split favoring reducing clinical events in the people that started early. And last were those with Framingham 10 year coronary heart disease risk. Above 10 percent, there seemed to be a big splay again favoring immediate over deferred. So, they concluded from this subanalysis, although we know that if you look at the entire population, people with CD4s over 500 do benefit clinically by starting early rather than delaying, that's been published. But that the risk reduction appeared even more in these four groups.

[00:12:06]

Age over 50, viral load over 50,000, ratio less than 0.5, or Framingham score greater than 10 percent. So, they suggested that those patients might be prioritized to start ART if you do need to do that and you have that choice.

[00:12:25]

What to start? Still a question that we think a lot about. So, there were new data about what to start. One of the analyses was again from the START study and that looked at the association of efavirenz, which as you know, is the most common antiviral worldwide. In terms of regimens, efavirenz-based regimens are number one and recommended by the WHO for all HIV-infected people.

[00:12:54]

They looked at the link between efavirenz and suicidal behavior. If that sounds familiar, there are published data from the ACTG. We were actually part of this analysis which looked at four big randomized studies and did find a significant association between those two facts.

[00:13:12]

Here's a follow up analysis from the START study which looks at the same thing.

[00:13:18]

Again, I just showed you the study design. So, above 500, start right away or defer.

[00:13:23]

And here are the end points here. Immediate is in red again and deferred is in blue. So, if you look at the primary endpoint, these were clinical, you can see 42 versus 96. That's a 57 percent reduction in clinical endpoints. That was the overall finding from the study, as you remember. Then they added other things;

grade 4 toxicity event, hospitalization, or death. And once again, you can see that numerically there were more in the deferred group, 311 versus 283 did not reach statistical significance. And then they looked at suicidal or self-harming behaviors and they found similar numbers, 27 and 24 in the two groups, which wasn't statistically different. But what's confusing about these results of course is that some of the deferred group actually goes on to start therapy and so many of them would have been placed on efavirenz, depending where they were around the world. So, they separated the data in a different way. So, rather than intent to treat, you know, once randomized always in that group, they looked at it as more of an as treated analysis.

[00:14:34]

Here are the composition of the suicidal behaviors that they saw. So, ideation, attempt, completed suicide, self injury, injurious ideations, so thinking about it, or intentional self injury. Again, in an attempt to treat, the numbers are pretty similar. But if you look specifically at people who are taking the drug in each group, so now they're censoring the deferred group after they start therapy, they no longer contribute to this analysis. The other thing to say about this of course is this wasn't a randomized study. So, clinicians and patients got to pick what they were choosing.

[00:15:12]

What you see on the right first, between the two arms the immediate versus deferred therapy, you really see no difference in the suicidal behavior group of diagnoses that they looked at. But then you look at people who pre-specified that they were going to use efavirenz and you do see a significant group. So, many more, I shouldn't say many, statistically more in the immediate group than in the deferred group. And that actually did reach statistical significance.

[00:15:43]

So, they concluded although it's based on a small number of events and that there were only 3 completed suicides, so many of the endpoints were actually ideation or attempted suicide, but they did find that participants using efavirenz in the immediate group had an increased risk of suicidal behavior compared to treatment naïve controls.

[00:16:09]

Okay, another study focused specifically on treatment naïve women and was conducted, an international study, and compared two common regimens we use today: dolutegravir, abacavir, and lamivudine. FTC is fixed dose combinations, so one pill once a day. And they compared that with the common regimen TDF/FTC and boosted atazanavir. So, this was a head to head comparative study called the ARIA study. Why was it called that? I don't know.

[00:16:42]

So, a big study, 705 treatment naïve women. They were randomized one to one, so one group got the dolutegravir-based and the other the boosted atazanavir-based. You can see that roughly 20 percent of women in each case withdrew from the study early, so about 80 percent completed in both studies. And these were the list of reasons why people withdrew early and you can see that it's sort of common

group of things: adverse events, lack of efficacy, protocol deviation, lost to follow up, etc. And not really different between the two groups.

[00:17:18]

The median age was about 37 years in the two groups. There was good representation both from women of African heritage, about 40 percent, and white women, about 50 percent, in each group. You can see only 4 percent had AIDS. About a third or a quarter to a third had viral load levels above 100,000 at baseline. And again, about half of the women had CD4s less than 350, so a moderately compromised group.

[00:17:49]

And here are the overall results. Let's focus on the solid bars, which are the intent to treat analysis. And what we're looking at here is the snapshot, so what percentage of women at week 48 had viral load levels less than 50, 50 copies per mil. You could see it was 82 percent of the women in the dolutegravir group versus 71 percent in the boosted atazanavir group and if you do the statistics on that, you can see that that certainly is non-inferior. It shows dolutegravir is non-inferior because it excludes the pre-specified minus 10 but it also, you can see the lower limit exceeds zero here, showing that dolutegravir actually fulfills superiority criteria to boosted atazanavir in this population of women. And that is highly statistically significant. What about resistance? There were very few women who had virologic failure.

[00:18:49]

You can see only about six in one group and four in the other and really no resistance in the dolutegravir group and only one woman in the other group developed an M184V. So, resistance exceedingly uncommon with virologic failure in this study.

[00:19:08]

And then in terms of adverse events, you can see drug-related adverse events about 33 percent in the dolutegravir group versus half in the atazanavir group. And what were the side effects? You can see a few GI things and then jaundice was not uncommon, as you'd expect, in the atazanavir group along with ocular icterus.

[00:19:34]

Overall, they concluded that in treatment naïve women the dolutegravir regimen was superior to the boosted atazanavir regimen at week 48. The safety profiles and the resistance profiles not significantly different. Here's an interesting study going back to the old question of we use three drugs for everyone. Might there be a patient population that would benefit from using four drugs at least initially?

[00:20:03]

And so, this was called the REALITY study and it was a 12-week study of using raltegravir intensified three-drug therapy versus standard three-drug therapy in adults and older children.

[00:20:19]

So, they picked treatment naïve adults. This was an international study of children above the age of five with profound immunosuppression. They all had CD4s less than 100. Again, the hypothesis here is if we use four drugs in this group, would that lead to clinical benefits? So, they were randomized one to one. One group got two nukes and a non-nuke, which is the standard of care arm and one got the same two nukes and a non-nuke but then added raltegravir as a four-drug regimen. The baseline demographics, it was split.

[00:20:55]

Well, first of all you see what a large study this was, 900 patients in each group. About half were men and half were women. You could see relatively few children, only 4 percent were children. So, this really turned out to be an adult study rather than a children's study. Recall again their baseline CD4 had to be less than 100 and you can see over a third of them were actually less than 25, so really quite a compromised group of people. Three quarters had viral loads over 100,000. You can see that although left up to the individual investigators, efavirenz-based regimens were the most common used. 90 percent of the people on the study took an efavirenz-based regimen and 80 percent took TDF/FTC as their nuke backbone. So essentially, this is a study of TDF/FTC and efavirenz with or without raltegravir. Does it make a difference? What do you think? Here we go.

[00:21:54]

When you look at less than 50 copies, if you look at week 48 you can see 80 percent of all patients regardless of the treatment arm made it to less than 50 copies. As you would expect, in the green arm is the raltegravir arm. That goes to negative faster, as we're used to seeing with integrase inhibitors. But everyone ends up in the same place by week 48.

[00:22:19]

CD4 changes. You can see down here they are overlapping, the two arms, and so by the end about 150 cell increase over baseline. The most important thing they were looking at was all cause mortality. Again, the hypothesis here is if you use four drugs in this highly immunocompromised population, might that lead to a clinical benefit in reducing mortality? And you can see from the back of the room, there was no difference between the two.

[00:22:49]

So, they conclude standard therapy works well and there is no benefit to adding the fourth agent, even in this highly immunocompromised group. So that was the should we add more? And this study was the can we use less? for the initial study. So, this was a two-drug regimen that you've been hearing about dolutegravir and lamivudine, two drugs together. This is a pilot study from Argentina that you heard some initial results of at previous meetings. This was the 48-week study. It's called the PADDLE trial.

[00:23:25]

So, they took a very small group in Buenos Aires of treatment naïve patients who were adults. Viral loads were detectable, above 5,000 and importantly, they put a ceiling on this of 100,000. So, they had to be between 5,000 and 100,000. CD4s were over 200 and they had to be Hep B surface antigen

negative because of the regimen that they were about to use. So, this was an open label. They gave everyone standard doses, two pills, one of dolutegravir 50 and one of 3TC at 300. They tested 10 people and then they ended up enrolling a second cohort. So, the study I'm about to show you is only 20 people. It's a true pilot study.

[00:24:08]

They were 19 men and one woman, aged in their 30s. You can see the baseline viral load was about 24,000 copies and the baseline CD4 was 500 or so. And here's the results. This is the kind of study where you can show every patient's viral load at every time point, which is what they're doing here.

[00:24:30]

They've color coded it for you. So, yellow box means that the patient's gone to less than 50. And so, you can scan down and see that by week eight, all 20 people had gone to less than 50 and they've presented that previously. They actually presented the week 24 results at CROI. Everyone stayed suppressed and then they updated with two more time points to week 48. Now you see two people who are actually not less than 50. This patient had a serious adverse event, committed suicide, and then the other one I'm going to show you the data, but had a viral load rebound.

[00:25:10]

So, the adverse events, again, relatively well-tolerated. Apparently the suicide case did have a history of depression.

[00:25:19]

And this is the person that broke through. So, they went down nicely. You can see their beginning viral load was actually at the time they started slightly over 100,000. They suppressed to less than 50 and then go along and then pop up to 99, they confirm it at 246. Because of the timing of this, they just drew another viral load and then put the person on three-drug therapy but when that viral load returned it was only 61. So, they're thinking maybe this was just a blip but the person went on triple combination and went completely less than 50 again. So, was it a true failure of the regimen? You could debate. So, that's what they said. So, that's where we are with this combination.

[00:26:07]

Pilot data, not ready for prime time. I don't think anyone should be using this routinely. We have a study in the ACTG that I think was fully enrolled today of 120 people and we raised the viral load ceiling to 500,000 and phase 3 plans are being designed right now. So, stay tuned but don't try this at home just yet.

[00:26:31]

What about switch studies? Now, we're used to in our field that almost every switch study we ever see, people do okay either staying on what they're on or switching to a new regimen. This study is no exception. So, switching to a new-- that same combo, dolutegravir/rabacavir/3TC, all in one pill from a

PI-based regimen, another integrase-based regimen or a non-nuke based regimen. This is called the STRIVING study. I have no idea why.

[00:27:02]

Here's STRIVING. You come in on your regimen and you either randomize the switch to the dolutegravir one pill or you continue your current regimen. But here's what's clever about this: at week 24, the continuers also get to switch to the dolutegravir regimen.

[00:27:20]

Big study again, 841 people divided into roughly two groups. You can see they had good completion rates, relatively few adverse events, only about 4 percent altogether. And so, it was a well-conducted study.

[00:27:36]

And here's the overall findings. So, we're looking at the early switch arm. So, people were suppressed at 85 percent of people continued to be suppressed versus 88 percent in the other group.

[00:27:52]

And then if you continued, 92 percent continued to be suppressed.

[00:27:56]

Suffice it to say that the switch strategy in this study worked and that's what they concluded.

[00:28:02]

One of the things about meetings that we always look forward to is what are the new drugs and the new regimens that are being looked at? Raltegravir has a new formulation. It's investigational. It's not available yet.

[00:28:15]

But the milligram dose is 1200 milligrams and it is a once daily version of raltegravir.

[00:28:23]

So, this was the head to head comparative study. Everybody got TDF/FTC and then one group got standard dose raltegravir BID and the other got the new formulation once a day. So, that's what this shows. It is reformulated. It was a 48-week study.

[00:28:40]

And again, big. This time they randomized two to one, so twice as many people, 500, got the new formulation versus the standard at 250. Treatment naïve with viral loads at least a thousand. Again, a well done study. Fewer than nine percent of patients discontinued early so almost everybody completed. And here's the results.

[00:29:01]

From the back of the room you can see that the two regimens highly comparable and 88 percent in each group suppressed by week 48. So, the new formulation looks very similar to the twice a day formulation. How soon will it be available? I don't know.

[00:29:20]

What about other endpoints? Again, they were very similar. They saw very little virologic failure in either one of the arms. And that's what both of these slides show. So, it was a well tolerated and high performing regimen. Resistance testing. There were a couple of people who broke through.

[00:29:38]

And they saw raltegravir resistance mutations and M184V.

[00:29:44]

And then clinical adverse events were relatively uncommon in both groups. Well tolerated. A regimen we've had our eyes on for a while is an all perenterol regimen.

[00:29:57]

So, that is the investigational integrase inhibitor cabotegravir, which can be dosed by injection every other month, so every two months. And then rilpivirine, the non-nuke we have today but also dosed with its investigational injectable form. This was the LATTE-2 study. We've heard the earlier results and this was the subsequent 48-week results that were new presented in Durban.

[00:30:28]

This was the design of the study. In the induction period, everybody took oral cabotegravir, so it is available by pills as well, along with two nukes, abacavir 3TC for 20 weeks. And the reason they do that is to make sure people are tolerating the cabotegravir before changing the regimen, making sure there's no side effects. So these were people who are naive, CD4s above 200.

[00:30:53]

And here's the design of the study. So, they go on the oral regimen and if they're suppressed, then they're randomized to one of three strategies. One is cabotegravir and rilpivirine dosed every month by injections. The second was cab and rilpivirine dosed every two months by injections. And the third stuck with the oral formulation. Again, we saw the week 32 results at CROI and these were the week 48 results at Durbin.

[00:31:22]

Here's the bottom line. What proportion in each group are suppressed below 48 copies, so suppressed below 50 copies, and you can see the three lines are superimposed. So, all three regimens did equally well with 90 percent plus. As you can see from here, this is week 32 but durable to week 48 suppressed below 50 copies. So, that's good news because that means that this, although not available yet, this

could be a two injection regimen dosed every two months that is capable of continuing virologic suppression. So, that could come in handy potentially for some of our patients.

[00:32:03]

These are the results put another way. You can see high virologic suppression rates.

[00:32:10]

Very few virologic nonresponse, so people did well.

[00:32:16]

And very few episodes of virologic failure and essentially no resistance or very little resistance associated with any of the regimens.

[00:32:27]

The most common side effect, as you might guess, were injection site reactions. They tend to diminish over time although you can see that about 10 percent have Grade 3 or higher. Grade 3 is severe. Often these were temporary and resolved within a few days. Very few people discontinue.

[00:32:47]

The LATTE-2 demonstrates you can successfully maintain suppression with a two injection regimen given every two months. That might be where we're going in our field at least for some people.

[00:33:00]

I'm going to finish with prevention. There was some new news on prevention as well. This was kind of cool. So, you'll remember the partners PrEP study. It was one of the studies that they did in Africa with discordant couples. So, one was positive, one was negative and the positive one was not being treated because of the time the study was done. The negative one was randomized to PrEP or no PrEP and PrEP showed 70 percent plus efficacy in avoiding infections. That was one of the two studies that led to the approval of PrEP. They did something interesting with the same population and that is... I'll just show you this. They came to a point where they were going to offer the positive partner ART now with changing guidelines. And they wanted to know how they were going to manage PrEP in the negative partner and people thought well if the positive partner is suppressed, do we really need to give PEP-- or sorry, PrEP, to the negative partner. And that's still debated in our field if you really need to do that. But they came up with a neat thing.

[00:34:05]

So, if the positive partner elected to go on ART, they gave the negative partner PrEP but only for six months and then told them to stop. If the positive partner wanted to delay ART and not start, then they gave the negative partner PrEP until, if the positive partner ever did start, six months, again, a six-month overlap period and then said stop. And then they followed people along. And here's what they found. So, this wasn't a randomized study. All the positives were offered ART and all the negatives were offered PrEP according to the strategy I just told you. So, they didn't have a control group.

[00:34:48]

But they estimated in this group that there would have been 83 new infections. And what they actually saw were four new infections. So, they estimated from that that there was a 95 percent reduction using that strategy that they had come up with. Just a simple overlap just used for six months.

[00:35:07]

And then, when they looked at the four people who seroconverted, none of the four were actually taking PrEP, which again we've heard from multiple studies before. So, this is an interesting open label demonstration project that kind of begins to inform us well how might we use PrEP in an era when we expect that positive partner will be on ART and suppressed. Another presentation dealt with what's going on with PrEP in the United States.

[00:35:35]

And so, this is from 32 demonstration projects. They actually wanted to see well how is that compare with the clinical trial results. And so, they put it all together the seroconversion rates from all this and estimated that it's about .95 per 100 patient years and that's almost exactly what it's been on the studies as well. So, it seems to be doing as well in the community as it does in clinical trials. Look at this. This was impressive.

[00:36:06]

How many unique individuals, Americans, have taken PrEP. And the answer is close to 80,000 people are now taking PrEP or have taken PrEP at some point. And you can see, remember it was approved in July of 2012. And look at this. Not much going on, not much going on, and then we hit 2014 and it takes off and then you hit 2015 and it takes off big time. So, PrEP has increased markedly in the United States, particularly over the last year or two.

[00:36:39]

Men and women, it turns out all the growth is in men. Women have gone from about just under 3,000 to 7,000, so that's more than double. But men have gone from 3,000 to 35,000, so ten times increase in men. And this tells you the looking at the age.

[00:37:00]

The median age is actually 36. So, potentially we're not reaching the people we need to reach which are the younger younger men under the age of 30. The men tend to be older than the women.

[00:37:15]

And then I don't know if you can see this so well but it's the region and state use. So, the number one state for PrEP use is... You're sitting in it. It's New York. So, about 16 percent of the prescriptions across the country are actually in New York. Other big states: Texas, Florida, Illinois, and California. And then you can see the map that the number one city, you're also sitting in, is accounting for 3,000 PrEP prescriptions at least at the time of this data cut right here in New York. I presented a PrEP study, I'm going to be brief about this, looking at alternatives to TDF/FTC.

[00:37:59]

And this was looking at maraviroc based regimens. These are the original slides, as you can tell. We did it in women. This is the first PrEP study ever done in U.S. women.

[00:38:10]

We defined them as at risk. They had a history of condomless vaginal or anal intercourse with a man known to be positive of unknown serostatus. And the regimens were maraviroc by itself, maraviroc FTC, maraviroc TDF, or the control of TDF and FTC. It was a phase 2 study, so really looking at safety and tolerability.

[00:38:36]

Most people completed the study. Nineteen percent prematurely discontinued the study med but there was no difference among the four arms that we tested. So, we concluded that the four regimens were equally tolerable.

[00:38:50]

And then we looked at safety events. There were no significant differences among the arms.

[00:38:57]

And drug concentrations. About 65 percent of the women had detectable drug at week 24 and about 60 percent at week 48. Compare that with other studies of PrEP in women from Africa. These rates are better but certainly not perfect.

[00:39:12]

And then how many seroconversions did we see on the study? That's right: zero. So, no woman seroconverted on this study. Was that because the PrEP regimens were highly effective or because the women were not at high risk? We don't know the answer to that. Could be either. Speaking of, so the long acting injectables everybody's excited about them but one thing they do have is a very long pharmacokinetic tail.

[00:39:42]

Meaning once you give that injection, there's no way to get the drug out and you can have detectable levels. This is the rilpivirine injection. You can have them for as long as months and months afterwards. Ian McGowan, that was one person.

[00:39:59]

Ian MacGowan looked at seven people who were given a single injection and followed them over time and what you can see here, this is a year and this is two years and you can still detect this long acting rilpivirine in a majority of people. It was also detected in endocervical and vaginal fluid. And so, this raises concerns about these long acting agents.

[00:40:27]

They found quantifiable levels in genital tract fluids 18 months after a single injection. So, we are going to have to be careful. Last study. Now this created quite a stir. They actually had its own session and it was not in the original book so it was sort of like word of mouth. Did you hear about this session?

[00:40:53]

Uncovering the role of the vaginal microbiome in determining PrEP efficacy in women. What does that mean? So, you'll remember the CAPRISA 004 study. That was the very first microbicide study that showed a positive effect.

[00:41:10]

It was done in Durban, South Africa and they randomized women to a 1 percent tenofovir gel or a placebo and followed them over time. There were extraordinarily high rates of HIV infection but significantly reduced in the women that got the gel. So, they went back and looked. They had saved samples from this group of women and they did an analysis of the microbiome of the vaginal flora.

[00:41:36]

And they found something interesting. And that is that the tenofovir gel seemed to be most effective in the women whose vaginal microbiome had lactobacillus, which is common in the vaginal microbiome. But what the title doesn't say here but what turned out to be true, if a woman didn't have the lactobacillus, the tenofovir gel didn't seem to work. It's confusing, right? So, look here.

[00:42:06]

These are the women who were lactobacillus dominant and the microbicide had a 61 percent efficacy in preventing HIV. If the woman was not lactobacillus dominant in the flora, only 18 percent efficacy. Why would that be? They looked at it another way. So, they made sure that they confined themselves just to look at women who used the gel more than 50 percent of the time because adherence would be a confounder here.

[00:42:39]

But when they looked at that subset group, overall the gel worked 56 percent of the time. In the lactobacillus group, it was 78 percent effective. But in the non-lactobacillus group, only 26 percent effective. Again, same results. What's the deal? What's the connection? All right, this one bowled me over.

[00:42:59]

Tenofovir from the gel, topical is rapidly depleted if gardnerella is there. Or the way they set it from the podium, gardnerella eats tenofovir. Who knew? But not lactobacillus. So, that's very odd, right? So, they're looking at tenofovir in the supernatant and the group with gardnerella in their vaginal microbiome, the concentrations of tenofovir were reduced by over 50 percent compared with the group that had lactobacillus where they saw really little change at all in the tenofovir group.

[00:43:41]

What do we make of this? Nobody knew but people were breathless. They were astounded to hear these results. Many people began to make the jump oh, that's why tenofovir doesn't work for women for PrEP but of course this is topical. We're not talking about the oral agents. But got a lot of press, a lot of excitement and we're not sure exactly why that is. So, that's my rapid tour of Durban for you and I'll stop there.

[Video End]