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2018 CONFERENCE UPDATES FROM IDWEEK IN SAN FRANCISCO AND IAS IN AMSTERDAM

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2018 Conference Updates from IDWeek in San Francisco and IAS in Amsterdam
[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 their 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. We hope this recording of David Hardy's presentation, 2018 Conference Updates from Infectious Diseases Week in San Francisco and the International AIDS Society in Amsterdam, will be helpful to her daily practice. I invite you to join us in New York City for our live meetings in the future. 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 David Hardy, Adjunct Professor of Medicine in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine in Baltimore, Maryland.

[00:01:01] I just want to first of all say what a great opportunity it is to get to come speak here finally. What I am going to do today is I'm going to wrap up a little bit of what I was going to present from the International AIDS Conference in Amsterdam and then go into some of the highlights that came out of I.D. week and tell you more about what happened there. So I am going to just mention, I know that you guys may have heard something about cure a few programs ago, but there was one presentation in Amsterdam I thought was particularly noteworthy because it really kind of spanned the research agenda from basic science all the way to human trials. And that was this concept of what's called Alpha 4 Beta 7. Alpha 4 Beta 7 is what is called an Integrin, and Alpha 4 Beta 7 is a receptor on the outside of CD4 positive T cells which is responsible for helping them to home to the gastrointestinal tract. And of course, about 60% of all of our T cells in our bodies line our gastrointestinal tract, which is a good thing for keeping things out of our gut and get into the bloodstream. But it's also sort of a bad thing because what happens is, is that's where HIV goes immediately to destroy the CD4 cell counts right after initial infection. So what this study was doing is a monoclonal antibody was created to be able to block that receptor, and by blocking that receptor it decreased those cell's susceptibility to HIV infection, and also didn't always put them in a place where HIV infection was going to be very highly problematic. So there was two studies that were done in macaques to really show what this may be. In the first study, it was one that was really very exciting, as this study design really was all about the monkeys were infected with SIV and then they were given a dose large enough that would actually cause them to have significant infection. They were then, after they established infection, they put them on ART and suppressed the infection for about 13 weeks. And after they were on ART, they then gave them 1, 2, 3, 4, 5, 6, 7, 8 doses of this monoclonal antibody called anti-Alpha 4 Beta 7 or a placebo IgG. And then they took away therapy, as all good cure studies should be doing, to see whether or not this intervention made a difference.

[00:03:36] So when they did it in monkeys the first time, they actually found something very interesting. The monkeys that got the IgG there in the Byrareddy trial, on your left, demonstrated that the monkeys who got the Alpha 4 Beta 7 anti-integrin monoclonal antibody their viral load decreased, it is undetectable in the blue line there after they went off therapy, whereas the ones who just got the immunoglobulin went up. But then they decided to repeat that, and another group repeated it in a confirmation trial and unfortunately it didn't happen again.

[00:04:11] So in between this first and second trial, one of our best HIV doctors in the world, Tony Fauci, grabbed on to this idea and decided that because there's already a licensed Alpha 4 Beta 7 medication called vedolizumab, which is approved for treatment of inflammatory bowel disease, that he would actually try this in human beings. So he created a similar sort of situation in HIV positive people, gave them several infusions of vedolizumab while they were on ART for 22 weeks and then they stopped the medications with an analytic treatment interruption to see what would happen afterwards. So what the vedolizumab here is shown in the blue line, and what they showed there was the effect to time to viral load rebound was in fact no different than a historical control of a placebo from a therapeutic vaccine study. And as you can see, it didn't work unfortunately with a very insignificant p-value. So what it is kind of saying is that everything that looks great in a monkey, may not be so good. It could be tried in a human being and I show you this because HIV cure research is one of my major research interests right now, and I can just tell you that this is something that has a lot of money going into it, a lot of good people working on this, but it's going to take some time. It's going to take some time. There's nothing that's going to be simple or easy about curing HIV infection and the one thing that I learned from doing several clinical trials now in HIV cure, is that we're going to have to sort of push the envelope. We're going to have to push the envelope somewhere, we're going to have a lot of very courageous people who step forward for some of these trials that may in fact be somewhat of adverse events.

[00:06:01] So in Amsterdam, there are also a lot of studies about different kinds of adverse events for metabolic toxicities and cardiovascular disease. The one I want to point out is that, one of the big, big stories that came out of the International AIDS Conference in Amsterdam was that two-drug therapy worked. You guys saw the results of this trial back in August. The two Gemini studies were each 700 plus patient studies of individuals that were naïve to therapy, who were started on either just dolutegravir plus 3TC or dolutegravir plus 3TC plus tenofovir or Truvada. So it was three drugs, a classical sort of three-drug regimen versus a two-drug regimen. The bottom line from that study showed is that the two arms of the study, two drugs versus three drugs, were non-inferior and also the more amazing thing is that there were only four failures in the two drug arm and only two failures in the three drug arm with no resistance seen whatsoever. So one of the rationales of course for using fewer drugs and especially not and a second nucleoside analog is less toxicity. So this study did in fact demonstrate that when looking at that plasma and serum markers for renal function, in terms of looking at how much protein was being lost, that in all situations the proteinuria was decreased with the patients who got two drugs who got the non-tenofovir continued regimen all the way across. And the GFR actually went down less with those patients who got two drugs versus three drugs who didn't get tenofovir as well. And of

course this is occurring because it's tenofovir causing the problems. What this study also demonstrated is that when you look at what's called bone-turnover markers, and if Todd was still here he could tell you more specifically about these, but we can look at these things like alkaline phosphatase, serum, osteocalcin, procollagen one, N-terminal peptide, is that these are markers that the bone is being remodeled. Metabolically active. And in all situations you can see that that's happening more with the green bars with the three drug regimen containing tenofovir than the two drug regimen not containing tenofovir.

[00:08:18] So this is good news, but this is not proof that the two drug regimen is less toxic yet, because these are not clinical results and although these markers for both renal function and for bone turnover are done as a surrogate for clinical results we have yet to really see whether the two drugs is truly less toxic. Efficacy wise it seems to be very much the same as three drugs, but toxicity wise we yet have something more to find out.

[00:08:51] One other very interesting study I found in Amsterdam was this study that came from the Kaiser Permanente. And at this point these are three different Kaiser Permanente groups because you know they're all separate, Northern California, Southern California, and mid-Atlantic and all three of them pooled their patients and had a huge number of patients around 38,000 HIV positive patients and about 380,000 HIV negative patients that were matched. And the bottom line from this was basically what they found in this follow up of about 17 years, from 2000 2016, is that the incident cases of heart failure, not cardiovascular atherosclerotic disease but heart failure from validated algorithms by looking at their electronic health record which is actually a very good one, were significantly higher over time and they had a long follow up here in terms of the amount of time patients were followed, the study was over 16 years, that the fortunate patients who are HIV positive were having more cases of heart failure than those persons are HIV negative. Through the way that they can actually look at this, they evaluated HIV as an incident cause of this by doing a multivariable Cox regression analysis. And they just did it for lots of things, health system, calendar era, when the medications were being used, demographics, lifestyle, cardiovascular history, other comorbidities, cardiopreventive, medications use, and acute coronary syndrome. So what they really tried to do was to push aside everything that they knew could be causing cardiac problems, and this is what was left. And so I think this is something we need to be aware of, is that with this kind of long term follow-up being on the lookout for things like heart failure different than cardiovascular atherosclerotive diseases, that we need to be aware of as well.

[00:10:43] So the the take home message from these two, are that the combination of dolutegravir plus 3TC does avoid the TDF-associated renal and bone demineralization biomarker changes. These are biomarker changes at this point, they are not clinical changes, and we have yet to learn more about that. And certainly looking out for heart failure was a good idea.

[00:11:07] Amsterdam had lots of information about HIV and co-infections and the one I thought was kind of interesting here was sort of something that I know this has been reported from New York City here as well. And that is sort of a spin off or a secondary outcome of PrEP. Like most places around the world, Amsterdam also has its PrEP cohort called AMPrEP a demonstration project containing 376 HIV negative MSM and transgender women.

[00:11:39] And people actually are given the choice of taking PrEP daily or taking the PrEP on event driven, or the way that it was given in the IPERGAY study that was done in France and Quebec. And this is still ongoing it started t in 2015 and it will continue through 2020. And what they did in the study, in addition to the usual sort of things for following for HIV infection and STIs, is they look for hepatitis C as well at baseline and then every six months afterwards to really see what the effect of people being on PrEP did to hepatitis C because we know that's a very potentially sexually transmitted infection. Two major outcomes of this analysis was incidence rates of hepatitis C primary infection and reinfection and also to look at how the infections were clustering by phylogenetic analysis.

[00:12:31] So first of all what they found was that over this about two year period of time, there were 12 overall new incident cases of hepatitis C. Six of those were primary infections, brand new infections and six of those were reinfection of individuals who had it before, been treated, and got infected again. And basically that's what the graphic basically tells you there. The other thing that they found very interesting here was you look at this phylogenetic map of all the different hepatitis C isolates, you see in those clusters 1, 2, 3, and 4 in the light blue shading is that the HIV negative men who are getting hepatitis C and HIV positive men in this analysis were clustering together in terms of the viruses being very close together genetically. So this I think is really kind of bringing some closure to the story that when men are on PrEP, at least in this cohort and probably not using condoms, that the chances of hepatitis C infection and reinfection may be higher than what it was before especially in places where hepatitis C may be currently already embedded in the community where PrEP is being heavily used. HIV and STIs, as many of you have probably heard, for the fourth year in a row when the data came out from the CDC from 2017 the U.S. has now hit another, fourth year in a row, highest STD reports of any time previously. So in Amsterdam we got to hear from the European CDC or the ECDC which basically is showing the very same thing, that cases of gonorrhea and chlamydia are increasing dramatically. Syphilis is increasing, not so much so as before, and the only thing seeming to go down there in that sort of dark orange line is new cases of HIV. And this I think gives some sort of idea that we are doing a good job of preventing or stopping transmission of HIV, but not of other sexually transmitted infections. At least in Europe. Same thing when they broke down who was actually being diagnosed with these new cases, MSM showed the biggest uptick between 2013 and 2016 with men who have sex with women and women actually remaining pretty flat with a little tick up at the last couple of years.

[00:14:58] And the trends in gonorrhea rates by risk group again, MSM were at the highest proportion there 46% compared to about a quarter of those in heterosexuals in women and men. And so I think

what this also kind of points out is that what we're seeing here in the United States is being seen other parts of the world, especially in Europe in terms of increased number of STIs. HIV prevalence decreasing but STI prevalence is clearly increasing. And I think that's something that, what we have done through HIVMA is we have asked administration now to follow up on what the Surgeon General has said and to actually declare a state of emergency about STIs in the United States because of the fact that this is something that's has continued to get worse and worse for the past four years with new cases every year and even new cases of congenital syphilis that had not been reported for many, many years are occurring as well. So it's not just about MSM, it's about other individuals who are having babies and transmitting syphilis to them as well. So that I think is also something we should look at as a bigger epidemic than just in our country as well. HIV and tuberculosis, I know this is something that you guys probably don't get a chance to treat very much here in New York City thankfully anymore. But there was a very interesting study called the Inspiring Study that was done in sub-Saharan Africa. And the reason the study was so important was because of the fact that right now the primary medication used to treat people who are HIV positive as initial therapy, whether they have tuberculosis or not, efavirenz based regimen. It's been shown that efavirenz can in fact be used safely with a four-drug anti-tuberculous medication regimen including rifampin or rifampicin, because the two medications efavirenz and rifampin can induce each other equally so they actually do leave each other alone. This study was trying to look at dolutegravir and pharmacokinetically what has been predicted was that if you double the dose of dolutegravir, then you will be able to keep the high enough levels with dolutegravir by giving a BID in concert with a rifampin containing anti-tuberculous regimen.

[00:17:21] But no one had ever done the study to really prove it. It was all based upon pharmacokinetic data. So this was actually the proof in the pudding of showing that taking people who were diagnosed with tuberculosis were put on the four-drug regimen seen there in the orange and then blue, for the first two and then four months and then were started either randomised to either be on twice a day dolutegravir plus 2 NRTIs or efavirenz. After the TB therapy had finished and they got about an extra four weeks, then they switched them over to the regular dose of dolutegravir of 50 milligrams once a day and then looked at the outcome of what actually happened there. Overall what they found was that the response rates were not the highest you'd ever seen, but they were not different. They were about 69 people in the dolutegravir arm, 44 people in the efavirenz arm for analysis and the response rate in terms of undetectable patients at the outcome of this study, 75% versus 82%, but not different between the two arms. We know that it continued to work. The thing that was, I think the most different in here, was that there were patients who were dropping out of the study and it happened to be more of those in the arm that containing the dolutegravir, but these were not virologic failures they were discontinuations for other reasons primarily but not really significant problems with failure at the time. The other thing that this study told us was that pharmacokinetically, the levels of dolutegravir were high enough both before and after the dropping of the level of dolutegravir from VID to daily with and without the tuberculosis regimen. So this really proved that you can in fact use dolutegravir as a medication regimen in those patients who are also getting anti-tuberculosis therapy.

[00:19:10] And the last thing here was that the treatment outcomes for the TB were in fact very good, 88% cure for the dolutegravir arm and 91% cure for efavirenz. So with the second infection being treated there, it also was a win-win. Well the last thing I was just going to mention here is not only do we know we could use it twice a day with rifampin okay, that the virologic failures in dolutegravir, there were 2 but there were no treatment emergent mutations like we've seen with other dolutegravir regimens, 1 virologic failure with efavirenz with treatment resistance that was seeing good pharmacokinetics, well tolerated actually better than the efavirenz. And the other thing of course we always worry about when treating TB and HIV at the same time is IRIS, and what they found in this study was in the number of cases of IRIS were exactly the same between dolutegravir or efarvienz. And of course the concern there would be because the dolutegravir drops the viral load so rapidly that in these patients with very low CD4 cells and very high viral loads, that there would in fact be a higher rate of IRIS occurring, but it did not occur and there was no death caused by IRIS either.

[00:20:22] So wrapping that up I'm going to go on then to the IDWeek. IDWeek used to be called the IDSA Conference. Certainly it's really a seven day conference that covers pretty much everything infectious disease you can imagine, including HIV. So HIV prevention like you might imagine with same day antiretroviral therapy starts, or rapid ART starts, meaning same day treatment when someone is first diagnosed with HIV. A clinic, a public clinic, the Denver Metro Health Clinic set up a same day PrEP initiation, in a drop in STD clinic. And what they were doing in this clinic is that when someone came in to be treated for an STD, they also offered them PrEP at the same time. If they said yes, then they got the PrEP that day and went on from there. So in this pilot report from the study in which the patients who came in got 30 days of FTC tenofovir PrEP, no refills at that time, and then were given counseling from a study coordinator or PrEP navigator to schedule an appointment one month out. And they give the PrEP free on site from a pharmacy there, they also provide counseling. In the first analysis they reported on their first 100 patients, and what they found in this study, very interesting to begin with, that of those one hundred, 78 or about 80% came back for at least one PrEP visit afterwards. And about 57% attended two or greater PrEP followup appointments as well. There were no adverse events or abnormal labs reported in any of these 100 patients that were followed up. And so that actually shows I think that there is some safety and there is some follow up perhaps that might be better than what some people think of starting same day PrEP. Now what they also did was to kind of look at the demographics and these were in fact young, less than 30, primarily men 98%, just a majority of non-Hispanic whites but also Hispanic and non-Hispanic blacks as well. Median income was twenty four thousand dollars which was pretty low but in a range of 14 to 38. 62% had health insurance and 24% overall were Medicaid insured, the majority 75% did not have a PCP. But of course as you might expect 50% had GC, syphilis, or chlamydia in the past six months, it was an STD clinic. When they looked at different sort of predictors for attending greater than one PrEP follow visit, looking at race,, age annual income, insured versus uninsured, the only thing they found that really showed that was a good predictor was annual income and for each ten thousand dollars it went up, there was an increase 1.6 fold or about 60% increase in the odds of someone coming back for one or more appointments. So other kinds of demographics didn't make a difference at least so far in this first analysis of this study. But same day PrEP looks like, if you have the right sort of mix and the right sort of resources to do it especially to give the PrEP out for free and have counselors are ready to help, it can be done.

[00:23:41] Now many of you may already know about this because it's coming from New York City, but this is a first year results of implementation of an immediate PEP access program through a 24 hour 7 day hotline in New York City. Some of you may be involved in this more intimately. So as this works, on the algorithm there on the left side, someone calls the hotline if it's Monday through Friday 9:00 to 5:00, they speak to a trained patient navigator or a physician and get started on PEP as soon as possible. By coming to the clinic and getting started there with after hours, which of course occurs very commonly with PEP requests they speak to a trained on call physician. The PEP assessment is performed according to the New York State in the DOH guidelines. If the caller is found to be eligible for PEP, the patient navigator makes a same day appointment, gets them on PEP gets them on PrEP, and the clinic if it's after hours the physician calls in a prescription to a pharmacy for a PEP starter pack for the first three days and then they come back to the clinic when the clinic is open to finish the 28 days. And the patient navigator then calls afterwards the hotline caller or clinic the next business day to make sure that they attended and that they're following up and the same thing happens when the handoff goes back to the patient navigators well. So in this analysis it was pretty much the whole year of 2017, january to December, there were 1,278 calls. 47 were repeat calls so the number of unique individuals was 1,231. Bottom line here was that in the PEP hotline, over half these individuals were less than 30, 18 to 29, but a smattering of people who are older. But in this case they had missing data for age in over a third of patients. 40% white, 29% Hispanic, 17% black, and 11% Asian. The majority were gay, lesbian or homosexual. 20% were straight or heterosexual. 10% bisexual. Some were missing. I thought the interesting thing here was that PEP was found to be indicated in 91% of the people calling in. And over 99 percent got the PEP within 72 hours.

[00:26:01] So that's actually that the program didn't work pretty well being to identify these individuals and get them started within that three day time period that's important. The ones who call after hours get the phone prescription was 69%. Over half were getting it through off hours as opposed to calling and getting it at the clinic, which of course kind of makes sense because PEP calls oftentimes occur after hours on Friday nights that have to be acted upon right away because Monday morning is too far away. 96.3% picked up the starter pack that was prescribed. And there were some repeat customers because prior PEP use was seen about 19% and prior PrEP use about 9%. When they looked at predictors for PEP access less than 36 hours, by doing a logistic regression analysis, what they found was interesting that there was, I would say a bit of a higher predictor if you were male versus female about 77%. The private insurance versus uninsured didn't really seem to make much of a difference one way or the other. But in terms of treatment by phone versus in clinic showed a 76% better pick up and taking medication within 36 hours than those who were treated over the phone versus those who came into the clinic.

[00:27:21] So let's look at some of the studies about first-line antiretroviral therapy presented at IDWeek. There were several studies that were looking at the second year of analysis of many of these studies that we've already seen 48 week data on. One of them was the GS, Gilead Science, 1489 study which was comparing bictegravir/FTC/TAF to dolutegravir/abacavir/3TC, our first head to head

comparison of two different unboosted integrase inhibitors in treatment of naïve patients. Down at the bottom there it tells us that at 48 weeks the results actually showed that there was about a 92.4% undetectable response rate with bictegravir, 93% with dolutegravir. So in the second year and also at 40 weeks, it was noted that there was less nausea reported by the participants with bictegravir/FTC/TAF than dolutegravir/abacavir/3TC, 10% vs. 23%. When the second year, basically in the 48 to 96 week, the results basically continue to look good. 87.9% of patients remained undetectable in the bictegravir arm. 88.9% in the dolutegravir arm. Very few individuals breaking through having HIV RNA over 50 at the 96 week window. And again what you see there is that although the point estimate is favoring the dolutegravir arm, the 95% confidence intervals cross 0 so there it says that non-inferiority continues. In the patients that did have failure and there were very few of them, there were still in the second year no treatment emergent resistance scene. I think the last thing here is that the one thing that was shown here is that in the first 48 weeks nausea was more common in the patients who were given dolutegravir. In the second year it looks like the dolutegravir/abacavir arm still continue to have more cases of people complaining of nausea, statistically significantly different there. There were also greater increases in total and fasting LDL with bictegravir than with dolutegravir. Primarily because of the fact that what tenofovir used to do is to lower cholesterol but because TAF is so much lower concentration, it does not have the same effect as it does with tenofovir. But the same number of patients were actually put on lipid lowering agent, numbers fall. The changes in GFR and this was a nice comparison of TAF versus abacavir over a two year period of time. Now to see how TAF vs abacavir is affecting the kidney, and you can see that that blue and that orange line are really overlapping and both integrase inhibitors decrease or push down creatinine clearance, calculated creatinine clearance, because of the effect of a blocking in secretion in the proximal tubule. But those had very same numbers.

[00:30:22] So that was the second year of 1489. The DRIVE-AHEAD study which was a head to head comparison of two different NNRTIs, the classic efavirenz/FTC/tenofovir versus the new one, doravirine/3TC/tenofovir. Into the second year at 48 weeks we already knew that 84% of the doravirine patients and 80.8% percent of the efavirenz patients became undetectable. But there were in fact less neuropsychiatric side effects with the doravirine compared to efavirenz, as you might imagine. In the second year, the response rates as you see here, look kind of low. 77.5% for doravirine, 73.6% for efavirenz, still non-inferior not showing a difference of one arm over the other. But one thing this is different, that's important remember is that unlike our trials that have been done with dolutegravir and bictegravir, these trials are having patients be called failures if they have two viral loads over 50 consecutively. The other trials that we just saw before with the integrase inhibitors are doing above 50 but then above 200 for the second confirmatory. And that's why these probably have less good results in the outcome. When looking at other kinds of baseline analyses here, whether the patient had high viral load, low viral load didn't really seem to make a big difference.

[00:31:47] It seemed like in those patients however though that had less than 200 CD4 cells at baseline, there was in fact a greater number of patients that did not become undetectable with those patients who received doravirine, so that might be something to note. Unlike the integrase sub-study we just

looked at, in this trial there were six patients who developed resistance to doravirine, 13 who developed resistance to efavirenz. So these are not resistant sort of regimens as we probably should keep in mind. And there were small decreases in fasting LDL and non-HDL with doravirine but increases with efavirenz, and that's something that may differentiate these two NNRTIs, less resistance and less poor lipid effects.

[00:32:35] The other outcome that was seen in this study kind of other adverse events, and then as it was seen in the first 48 weeks there were more drug-related adverse events leading to discontinuation with efavirenz than with doravirine. And then this table to the right, you can see that the majority of those were in fact neuropsychiatric side effects such as dizziness, sleep disturbances, altered sensorium, depression, and psychosis being more common with efavirenz than with doravirine, which is I think something that isn't too surprising for any of us to see.

[00:33:05] Switching ART and virologically suppressed patients. Another trial that was done with doravirine, DRIVE-SHIFT study. Basically took patients who were on a stable regimen for greater than six months, had no history of previous virologic failure or history of resistance to any of the drugs, these patients were randomized to continue their baseline regimen which could in fact be a ritonavir of cobicistat boosted PI, atazanavir, darunavir, or lopinavir, could be elvitegravir boosted with cobicistat, or an NNRTI regimen. So it was really an all-comers sort of regimen that came into this. They were randomized to either continue on their baseline regimen or be switched to the single tablet regimen of doravirine/3TC/tenofovir, which is now licensed. At 24 weeks the patient that did not get randomized to begin with to the doravirine arm, were switched over at that point. And the way this analysis was done interestingly, is that they compared the 48 week arm outcome in the patients who were put on doravirine immediately versus the 24 week outcome in the patients that were randomized to the baseline regimen as the primary analysis. Secondary analysis looked at 24 weeks in both.

[00:34:18] So in looking at this, and I'll draw your attention to the bottom part of this slide, is that week 48 doravirine versus 24 baseline ART, proportion of patients that were undetectable 90.8% versus 94.6% but was not statistically different, because the upper and lower boundaries of the 95 percent confidence interval did in fact cross zero. The proportion of patients that failed were small, 1.6% versus 1.8%. And then at that head-to-head comparison of 24 weeks versus 24 weeks, again the same kind of results were seen as well. So this was I think something kind of important about looking at how this switch can in fact occur and be successful. And the other thing I think was important that was different here than the naive crowd we just saw before, was that there was no evidence of treatment emerging resistance in those patients that got randomized to doravirine. So at least in the situation where patients are switching from being undetectable to doravirine, resistance does not seem to be as much of a problem as it is when they start naive.

[00:35:23] Safety outcomes were again pretty much the same in both arms of the study whether it was an immediate switch, continued on baseline ART, or late switch. It was notable however that in terms of drug related adverse events there were 2 versus 0 and that's probably relating to the fact that when a patient switches over to a new regimen off the currently well tolerated baseline regimen, they tend to have side effects that you wouldn't get if you continued on the regimen to begin with, which is something that's kind of common to most switch studies.

[00:35:55] The next study we will look at, in terms of follow up, will be what's called the EMERALD study. And this is again the second year of follow up of EMERALD. EMERALD was a trial that took patients who were on a boosted PI, boosted darunavir or boosted atazanavir, and put them on either the single tablet regimen of darunavir/cobicistat/FTC/TAF or continued them on their baseline PI, who got switched later. So at 48 weeks what we had already seen was that the switch to the four-drug regimen with darunavir versus continuing, only should a 2.5% lack of maintaining undetectability or breakthrough viremia versus the 2.1%, which in fact met the boundary for what they had already established as the less than 4% for the non inferiority margin with the FDA. So in the 48 weeks, this study had reached non-inferiority, let's see if it maintained it. And in the second year, basically what happened was that there was continued good maintenance of non-inferiority in the second year of this. Remember that these patients are being switched over after week 48 in the arm that started off with the PI not darunavir. There were no resistance mutations to darunavir, tenofovir, or FTC, or any primary resistance associated mutations for PIs from post-baseline. So again this continues to be a good idea.

[00:37:35] Safety outcomes were pretty much the same both arms of the study. There were changes in BMD in both arms because this is looking at a boosted PI and those seem to have more problems and it doesn't matter whether it was darunavir in the four-drug regimen or the baseline PI, they actually caused the same kind of thing.

[00:37:54] Now the other thing that they looked at and that was reported at ID Week was sort of a new and different sort of look at the effect of in-utero antiretroviral exposure in infants who were born to HIV positive mothers but who did not become infected. So it is called HIV exposed but uninfected infants. And this SMARTT study is the longitudinal observational cohort designed to assess the adverse events related to in-utero ARV exposure. Done in multiple sites in the US and in Puerto Rico. And what they actually were looking at in this analysis was the measure, the rate of neurologic conditions in the SMARTT cohort. They were really looking to see whether or not they could find something associated with efavirenz, as other studies have done like the one from Botswana, and assess the relationship between ARV exposure, neurologic conditions, and follow up for different kind of confounders. So this was run from April 1st 2017 to August 1st 2017 and the primary outcomes were a neurologic case, was defined as microcephaly, febrile seizures, seizure disorders, ophthalmologic disorders, other neurologic conditions. And this was actually curated by a blinded clinical review board. So the bottom line here was that there were 3,747 HIV exposed but uninfected children for neurologic evacuation. Of those, 6.3% or

287 neurologic cases were found. ARV exposure in these 287 neurologic cases were 70% PIs, 19% NNRTIs, and 4.5% of them being efavirenz. Overall 11% integrase inhibitors but only 2.6% were dolutegravir. They did also notice that in the analysis there were other confounders, such as tobacco and alcohol use, which did in fact have a significant effect on increasing risk ratio for neurologic conditions. And as you can see the most common thing here was microcephaly followed by febrile seizures and then eye abnormalities and epilepsy. There was a very broad look at different kinds of neurologic abnormalities. When they looked at this based upon different in-utero exposures to different antiretrovirals, they found that efavirenz exposure was not significantly associated with neurologic diagnosis in the primary analysis. However in-utero efavirenz exposure was significantly associated with increased risk in 4 sensitivity analyses, including the exposure at conception versus no exposure whatsoever. So overall it didn't look like efavirenz had a great effect but when they broke it down into other smaller kinds of sensitivity analyses, they did find at least one significant p-value. The thing that was sort of surprising and this really came on the tail of the neural tube defects reported last spring then again this summer at Amsterdam, was that there was a possible association between in-utero dolutegravir exposure and risk of neurologic diagnoses. But it didn't quite reach statistical analysis in this particular evaluation. So I think this is something that as you look upon this table on the right side, of looking at adjusted risk ratios for neurologic diagnoses in the primary analysis versus the first trimester exposure, conception versus no conception, there were a few places where you would see close but not statistically significant differences with dolutegravir even being higher many situations than with efavirenz. But the number of patients with dolutegravir is so small that it is probably not really adequate to really give a good evaluation of this, but something to keep an eye on as time goes on.

[00:41:47] Treatment-experienced patients. This study was I think kind of interesting because it looked at a strategy that some of you may already be using in terms of taking your highly treatment experienced patients and switching them to boosted darunavir plus dolutegravir, a two-drug regimen. And so in two different HIV clinics in Denver between December 2013 and December 2017, they took individuals who were in a case where they needed to be put on a regimen that was more simple to be able to see whether or not they could get them and keep them undetectable. 49 of these patients were undetectable, less than 200, at the time of switch off whatever regimen they were on to the dolutegravir plus boosted darunavir and 16 were detectable. The median duration of previous antiretroviral therapy was 19 years. So these were definitely those legacy patients that many of us still have in our practices. 85% had been on an NNRTI, 89% had been on a PI, and 57% had been on an integrase inhibitor. And there were 5 patients that don't have previous darunavir resistance associated mutation, shown there in the parentheses. So the reason for switch is primarily because they already had tenofovir experience and they could not go on tenofovir, they had abacavir resistance or it was contraindicated, or the fact that they had resistance or intolerance of other regimens, or chronic kidney disease. So these were basically patients who had really worn out the nukes, had adverse events to them and had lots of mutations to them as well.

[00:43:27] So what it really showed here was those patients that started off on detectable, there in the blue line at the top, at baseline pretty much remained undetectable on this two-drug regimen of dolutegravir plus darunavir. Over that greater than one and a half year follow up, those patients that were detectable at baseline actually did reach, about 80% initially kind of bumped up and down between 70 up to as high as 83%, dropped a little bit at the end there to 76% but again probably better that proportion of individuals that are undetectable less than 200 than what they were before when more of them were detectable. So I think this is something that is kind of nice to see is that an analysis has been done of using this kind of two-drug regimen in patients that are certainly high treatment patients with a very simple two-drug medication once a day.

[00:44:24] Comorbidities and other outcomes. There was interesting trial here about unmet needs among patients living with HIV as barriers to retention in care and virologic suppression. So the MAPPS study was a trial done at several sites around the country, in terms of looking at patients living with HIV infection who were hospitalized between August 2010 and August 2013 and who are not meeting the definition of being in care. In care meant that they had three consecutive, at least three consecutive, HIV RNAs less than 400 for the previous six months and attended HIV primary care visits greater than three times in the previous four quarters, in previous 12 months before hospitalizations. So individuals who were not undetectable and those that had not been to primary care clinics. Patients who were diagnosed with HIV in the hospital were also eligible for this study and they looked at both unmet subsistence as well as medical needs by self report at baseline and three months. And there were two primary outcomes that they were looking at here, improvement in viral load by at least dropping it by a log or becoming undetectable less than 400, or in terms of care retention completing greater than 1 primary care visit in the first month after being discharged from the hospital. And then 1 primary care visit in the next six months as well. The bottom line from this study is not too surprising, they had 417 patients, was that they found the most common unmet needs were dental care, financial assistance, and housing. And those patients with unmet needs versus those without any needs at baseline more likely to be African-American or black, have a preexisting HIV diagnosis, and to be uninsured. So this actually in many ways I think proved what many of us have already noticed for many years. But in a way it really showed it even more more carefully. In terms of subsistence needs which are defined as housing, food, financial, transportation was that the greater the subsistence needs the lower the chances that someone is going to have undetectable virus or be retained in care. As you might expect the number of greater subsistence needs unmet, the greater the chances they are not going to be undetectable or have enough visits to qualify for what's called retention in care. And then medical needs defined as mental health, substance misuse treatment, adverse event information, assistance with medications, or case management and dental care had the same kind of results as well. There was a drop in patients who became undetectable or retained in care, the greater number of medical needs that were being unmet.

[00:47:09] Again I think this really kind of pinpoints the fact that at least in this cohort, the things that we oftentimes don't look at in terms of unmet needs are probably some of the most important. And I

was going to show you this last slide about weight gain because it was also presented at IDWeek by Jordan Lake. And the last thing I was just going to mention here is the fact that this was a cohort analysis that over time ofA.R.T. API or integrates treat treatment. What they showed in these three groups of NNRTIs, PIs, and integrase inhibitors, they did a five year analysis of the weight of these individuals and they all started off right around 79 kilograms so they were not small people to begin with. And what they found over time was that as you can see in the NNRTI group there they went from 2.6 at one year, 3.3 at two years, and 4.1 at four years, kilograms of increased weight. But in the PI and the integrase they actually went up more. And the analysis there showed that there was no significant difference between integrase and PIS, but with the other 2 integrase versus NNRTIs and PIs versus NNRTIs there was. So whether this cohort study tells us enough about this integrase, is really being the one that is making a difference? But the PIs did the same thing as well. I'll end there and say thank you very much.

[End]