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# HIV DRUG RESISTANCE: A REASSESSMENT

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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 co-infections and complications. We hope this recording of Dan Kuritzkes presentation HIV drug Resistance of Reassessment will be helpful to you and your daily practice and 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. Membership is open to all interested clinicians nationwide on our website. PRN.org. Now allow me to introduce Dan Kuritzkes professor at Harvard Medical School and chief in the Division of Infectious Diseases at Brigham and Women's Hospital in Boston Massachusetts.

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So looking out at the audience and not wanting to make any presumptions I would guess that the majority of you were not doing HIV medicine in the bad old days but in the era of mono and dual therapy failure to achieve full suppression of HIV replication invariably led not only to the accumulation of resistance to the first drug that was being administered but to the accumulation of mutations which conferred broader and broader cross resistance within the class and the addition of single active new agents as they became available led to what was essentially serial mono therapy. So people had been treated with either Zydovudine or Didanosine or Stavudine and then they added Lamivudine when it became available and then they added either Indinavir or Nelfinavir or Saquinavir when those became available and one after another people became resistant to all of these drugs and that led to huge generation within individual patients of multidrug resistant virus which was then also being transmitted to their sex partners or to people with whom they were sharing drugs. Exacerbating the problem and to get a sense of how significant this was and this is now going back 12 years these data from Andrew Philips from from London looking at the sheet cohorts where they showed that within two years of starting antiretroviral therapy of about 7 percent of individuals had resistance to at least two classes and by six years that was close to 20 percent with about 5 percent having resistance to three classes.

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Now this didn't necessarily mean resistance to all drugs because if you had a 3TC resistance mutation that would count as resistance to one class and if you hadn an Efavirenze or Nevirapine resistance that would be two classes but that still potentially left the protease inhibitors available or you could be resistant to Indinavir or Nelfinavir are and still be susceptible to Lopinavir. So these data tended to overestimate the seriousness of the issue but it nevertheless was quite significant that just under 40 percent developed resistance over six years and mutations to any drug. It was about a quarter of the

population. But if you look to for true triple class drug resistance that was accumulating much more slowly and again these are data from a couple of years later from Andrew Phillips and the same chic cohort. And you can see that after a decade only about 10 percent had triple class resistance.

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And I have to emphasise again that having resistance to a drug within each of three classes didn't mean that all all drugs in each of these classes were no longer effective and of course at this time all we had were three classes.

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This was before the advent of the integrated inhibitors and the second generation nukes and the and the entry inhibitors.

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So the folks at the CDC have done a terrific job of surveying the transmission of resistance.

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They've done that really by looking at Sentinel Centers where they do HIV testing and then for those individuals who are newly positive for HIV reflexing those same samples to do genotypes for HIV drug resistance. Now of course these people who test positive are a mixture of people who are recently infected and people who've been infected for some time but have finally decided to come and be tested. And so it's a little bit challenging to distinguish who has recently acquired HIV drug resistance and who has been carrying virus that is HIV drug resistance that was transmitted some time ago. But the important issue here is the trend and you can see that in the 12 years from 1998 to 2010 there was a rough roughly three fold increase in the prevalence of any drug resistance among the newly diagnosed but there was also a shift in the pattern. By 2000 the majority of transmitted drug resistance appeared to be resistance to the nucleoside reverse transcriptase inhibitors and this was almost uniformly resistance to AZT or Zidovudine and the other nucleoside analogues that were shared cross resistance with Zidovudine. And that resistance then began to diminish as the non-Nucleoside RT inhibitors especially efavirenz became commonly used as first line therapy. And so by 2010 the predominant form of transmitted resistance was to the non-nucleoside RT inhibitors about 8 percent and PI resistance remained relatively less common and dual class or more resistance was still relatively infrequent.

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Looking a little bit more recently and here you can see again the same these sentinel cities in which these surveys were done overall resistance still hovers around 16 or 17 percent with again and an RTI resistance predominating and nucleoside protease inhibitors resistance being far less common.

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But there's a lot of regional variation and here in New York City and these data were presented just two years ago at the retrovirus conference and here they've stratified those who have acquired HIV relatively recently versus those who were thought to have long term HIV infection. And you can see that among the recently infected more than 20 percent actually had evidence of transmitted resistance compared to 15 percent of those who had a longer term infection. Margo and colleagues at Gilead have analyzed the resistance patterns in participants or candidates screening for entry into phase three clinical trials that were done the 903904 were two different tenofovir studies and then the 104 and 111 studies were more recent studies looking at newer antiretroviral drugs and you can see these data quite closely mirror the data from the CDC showing that whereas in a previous decade and in RTI resistance in 2000 was relatively uncommon.

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It became somewhat more common in 2003 and was fairly common in 2013 nucleoside resistance especially the Thymidine analogue mutations are those that confer resistance to AZT and other nucleosides have been reasonably steady at somewhere between 2 and 3 percent of protease inhibitors resistance remains relatively infrequent and integrase inhibitor resistance was really quite uncommon.

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Well why do we care so much about transmitted HIV drug resistance. There was the assumption that resistance contributed to treatment failure and we were finally able to demonstrate that this was in fact the case at least so far as transmitted non-nucleoside resistance is concerned and that these are data from an old ACTG trial that looked used Efavirenz based regimens and the study was conducted in era prior to the recommendation that resistance testing be done before initiating antiretroviral therapy so we had the opportunity in the study to go back to the baseline samples and in a case cohort designed sample a subset of randomly selected subset of the participants determine how many of them had and an RTI resistance. And how did they fare compared to those who did not. As you can see in the black line if you had an RTI resistance you were really about two and a half times more likely to fail compared to those who had no resistance. And these data contributed in large measure to the DHHS recommendations and the guidelines. Now to perform HIV drug resistance testing prior to starting therapy we went a step further than in John Lee in my group did an analysis for which was actually a

pooled analysis of 10 different studies from around the world where he was able to get patient level data and look at you.

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These were studies that had used much more sensitive techniques that could find the presence of minority drug resistant variants or variants that might not have been picked up by routine sequencing and ask if you had the presence of a resistant variant for nevirapine or Efavirenz resistance and you received a nevirapine or Efavirenz containing regimen what was the consequence. And again very much like in the previous slide I showed there was about a two and a half times greater likelihood of failing. But there are a couple of things that are notable here. First of all not everybody failed 60 percent of the people with minority variants were still successfully suppressed which has made it really very challenging to argue that there's any rational cost effective basis for trying to do screening of patients for minority variants because if the majority are still going to get suppressed and it only mattered if you had an Nevirapine or Efavirenz of resistance because we could not demonstrate any significance to having minority nucleoside resistant variants then you really couldn't make a recommendation to go to more sensitive assays. It was also clear that not everybody who had susceptible virus was going to be successfully treated and that was mostly because of challenges around adherence when when John looked at this more quantitatively what he found was that there was clearly a there was a statistically significant trend. So if you if you asked. How what percent of the population was resistant and how much virus was in the sample and you multiplied the percent times the virus you could come out with a number that was how many mutant copies were present per mil of of plasma and there was a statistically significant trend.

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So that if you had one to nine copies of mutants you had about just a little under a two-fold risk of failing and if you had more than a thousand copies of them and you had a four-fold risk of failing and that was quite significant but again this was only relevant for the non-nucleoside or RT inhibitors.

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Well I've just spent all of his time showing you how resistance used to be important why is it no longer so significant.

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Well first of all the prevalence of resistance overall in people failing antiretroviral therapy or in resistance tests being submitted to various commercial laboratories for testing is actually has been been falling over time if you look at triple class resistance so here you can see that non-nucleoside resistance

has been on the rise in that but has stabilized and that's clearly because of the previously widespread use of the Efavirenz as a first line therapy. But if you look at the presence of dual resistance to nucleosides and non-nucs or to the presence of protease inhibitors or a nucleoside or protease inhibitors a non-nucleoside or RT inhibitor resistance that has been on the decline as has the prevalence of triple class resistance. So the kinds of people we were generating back in the mid 1990s through the early 2000s people who were failing one regimen after another simply not happening with any significant frequency anymore largely because our regimens are better they're more convenient they're far more potent they're less likely to select for drug resistance and we really have dichotomized our patients for the most part not exclusively but for the most part to those who are taking therapy reliably and are suppressed and those who simply are not taking their drugs. This is also seen in the data from Scherrer at all from from Switzerland.

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This is a little bit more complicated to follow but essentially what you're looking at here are the number of individuals on antiretroviral therapy over time overall and then broken down by era and there was a bit of a dip here because this is when there was a lot of controversy about when to put people on antiretroviral therapy and then in the green is those who are ever experienced biologic failure in the yellow or gold were those who had a genotype after treatment initiation. The red shows those who ever had resistance detected and then the green is those who ever had three class resistance detected. And what you can see is that overall as the numbers of people being treated for HIV have increased the proportion with resistance has actually flattened out and those with triple class resistance has remained relatively uncommon and most notably in the last six or seven year period shown here. There was a dramatic escalation in the number of individuals on treatment with virtually no increase in resistance. So the resistance problem that we had in the past when we were generating lots and lots of resistance because of inadequate therapy and always trying to do the next best thing but always being somewhat behind the curve with our regimens has fortunately become a thing of the past at least in economically advanced countries like the United States Western Europe and Australia.

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Well what about transmitted resistance to drugs other than the nucleoside RT inhibitors so. Anna Maria Gianetti who is also in London did an analysis where she asked what's what is the significance of having transmitted nucleoside reverse transcriptase inhibitor resistance and does it matter whether you getting a non-nucleoside RT inhibitor or protease inhibitors based regimen and that this is not a randomized study this is a cohort study so the comparison between the non-nucs and the PI has to be taken with a bit of a grain of salt but you can see that the solid lines show the treatment outcomes in the absence of any transmitted resistance blue being non-nuc regimens and red being PI regimens and the dotted lines show the presence of isolated thymidine or AZT resistance mutations and again AZT resistance confers resistance not just to AZT but if enough mutations are present confers resistance as well to D4 TTDI tenofovir and even some cross resistance to 3 TC and the two surprising findings here were one the not-

nucs actually outperformed the boosted PIs. But again not in a randomized setting but there was no significant difference in the rate of failure. If you had resistance compared to not having resistance even though these are slightly more common that wasn't a statistically significant difference so having transmitted nucleoside resistance as compared to transmitted and an RTI resistance had really minimal impact on the efficacy of the antiretroviral regimen.

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This was shown in greater detail in a paper published in The Journal of Infectious Diseases earlier this year again by Margot at all from Gilead whose some of whose data I showed in a previous slide and what they looked at all of their studies that involved elvitegravir of your or rilpivirine where participants received either the older TDF formulation or the newer TAF formulation of tenofovir and they compared they looked at them and again the randomization here is not between TDF while in some of the studies there was randomization between TGF and TAF but the comparisons or importance are between presence or absence of resistance. And so if you look at the two lines here that compare having nucleoside RT inhibitor resistance or not. You can see that whether you got TDF or TAF having transmitted resistance made no difference if you got rilpivirene. So here in these studies you were allowed to go into a rilpivirene study if you had a 1 to 3 mutation because the rilpivirene is effective against the one to three ends.

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You couldn't go in with other mutations but it made no difference if you had that transmitted resistance. And here that shown in more detail in the no real difference. Likewise just as I showed you in the data from London if you had transmitted nucleoside resistance or not it made no difference in terms of treatment outcome of whether it didn't matter whether you got TDF or TAF if you had Tam's specifically so that the nucleoside resistance includes 184V would include. There were you couldn't get in with a 65R really so these this category is essentially TAMS plus 3 TC resistance or FTC resistance. And here is just limited to having TAMS and there was no difference. And here they're looking more particularly at revertant mutations because if you've had transmitted resistance and you're not on the drug the mutations tend to revert and some of them don't revert all the way and yet again you find no effective resistance on an outcome even though transmitted even though AZT resistance if sufficiently high level is known to confer cross resistance to Tenofovir. It made no difference in the outcome of the regimen and of course as you would expect there was no effective transmitted P.I. resistance. A couple of the studies were comparisons of elvitegravir without atazanavir and or rilpivirene with the boosted PI. So again the bottom line is transmitted nucleoside resistance really makes little difference.

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If you're looking at contemporary regimens it's also clear that we're much less likely to select for resistance in at the time of treatment failure. This is a compilation of studies that include looked at a

variety of boosted darunavir of regimens and you can see here in this column the number of participants who had protocol defined virologic failure. Each study had a different definition but there were just under 200. In aggregate nearly all of them successfully had resistance testing done and of that nearly 200 only.

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Only four had any evidence of having developed a protease inhibitor of resistance mutation. Whereas only 10 developed resistance to a nucleoside there were some of these studies like those that contained after virene. There was the opportunity to develop and in RTI resistance and two participants did so so again in contrast to what we were seeing in the 90s in the early 2000s where treatment failure was almost always associated with with the emergence of drug resistance with contemporary regimens treatment failure is really infrequently associated with drug resistance to the extent that when I first moved back to Boston 15 years ago I was asked to run a resistance clinic at Mass General where I would precept the HIV fellow once a month to be to review drug resistance test results and I haven't done that for the last seven or eight years because there is simply not enough. Patients with interesting resistance patterns that are worth sitting and looking at and it's simply and even in our own practice at the Brigham. It is a rare occasion where a colleague comes up to me and says Gee I have this really complicated resistance pattern what should we treat the patient with.

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ACTG 5257 compared raltegravir to two different boosted P.I. regimens boosted darunavir and boosted atazanavir.

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And although we saw 3TC resistance in each of the arms at the time of protocol defined failure finding resistance to the boosted PIs was quite uncommon. One and a half percent atazanavir and less than 1 percent of darunavir and only 3 percent to raltegravir in the raltegravir of your arm. So again very uncommon to find resistance at the time of treatment failure. This is partly because we're better at identifying treatment failure and moving quickly to change regimens and partly because of the regimens are far more effective than our previous regimens used to be. The same is true with elvitegravir here. In this study that compares to efavirenz to elvitegravir you can see that there were first of all relatively few failures out of the 700 people in the study there were 14 elvitegravir failures and 17 efavirenz failures. Only 2 percent of the participants overall are roughly half of the failures had evidence of elvitegravir of year resistance and about the same proportion had evidence of resistance to efavirenz in the comparator arm. Resistances even less likely to occur with dollar UTECH Revere. This single study compared the use of dolutegravir with the back of your 3TC to the triple drug formulation of efavirenz and tenofovir and FTC and you can see there were comparable numbers of protocol defined biologic failures in each arm and similar numbers that were able to be genotyped.



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There was no evidence of resistance to any of the components of the regimen and the dolutegravir arm where there was as expected resistance to the nucleosides and the non-nucleosides in the efavirenz containing arm.

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More recently the data have been presented on big tegravir another integrase inhibitor that is still investigational but that's expected to be FDA approved sometime within the next year. And this study compared big tegravir FTC and TAF dolutegravir FTC and TAF again just under 700 participants in the trial overall very small numbers of treatment failures overall and no resistance in any of the people failing.

[00:25:03] The same was true in the companion study which looked at the same regimens but this time given as a single tablet regimens for the dolutegravir arm and again very small numbers. Now here just over 600 participants and virtually no failures and no detected resistance.

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That doesn't mean that you can't generate dolutegravir resistance if you don't try.

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And I think just as just as was true in the previous era there's a right way and a wrong way to give antiretroviral therapy and the right way is to give it as part of a triple drug regimen and the wrong way is to give it as monotherapy. And so the study was done. This was an international multi cohort retrospective study. So it's not that people got together and set out to give monotherapy but in different Europeans and Canadian centers there were enough people who had been using monotherapy that they decided to pool the data. These were all of people who were switched to dolutegravir monotherapy given once daily and had at least one follow up visit after starting on monotherapy. And at the time that they switched to monotherapy had to be suppressed as defined by a virus load of less than 50 copies they were excluded from this analysis. They had prior failure on an integrase inhibitor containing regimen with selection of resistance and actually when I show you the next slide you'll wonder just how rigorously these inclusion exclusion criteria were applied and they also did not include any individuals who were in a randomized clinical trials of dolutegravir. And what I hope you can see on the slide here is that first of all in about 45 percent of individuals dolutegravir was their first integrase inhibitors. That means the majority of people had been on it either, raltegravir or elvitegravir before and had switched

dolutegravir presumably while suppressed and nearly three quarters had been suppressed for at least three years.

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Adherence was less than optimal in in four of the 11 and then the median time from virologic failure to genotype was about 5 weeks so they had some opportunity to do the testing while they were on therapy. But what you can see is that in these 11 participants there were nine of the 11 had evidence of selection of a and integrase inhibitor resistance mutation. None of these in this case were the classic 263 mutation that has been identified by Mark Weinberg as the canonical dolutegravir esistance mutation. But all of these are mutations that have been associated with resistance to raltegravir elvitegravir so that even though the 155 mutation for example by itself does not confer resistance to dolutegravir it was nevertheless selected by dolutegravir as was the combination of the 92 or 97 mutations with 155 while were more used to seeing as the 148 140 S combination that is sort of the stepping stone to high level dolutegravir resistance after raltegravir failure. So the and this is the time to resistance here ranged from almost happening right away to taking six months or so. Or or as long as 72 weeks a year and a half to occur in this case there was no resistance that was detected. So the bottom line here is that even a drug that appears to be unaffected by by drug resistance can be caused to select drug resistance if used inappropriately and we've seen the same thing with boosted P.I. regimens as well.

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It's rare to see boosted PI resistance in people who are either taking the drug or not taking the drug but if somebody is persistently intermittently on therapy then you certainly can see resistance and resource limited settings especially where low boosted lopinavir used in combination with rifampicin as part of a TB regimen and the lowering of lopinavir levels. You can see treatment failure with the emergence of lopinavir resistance.

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So where does this all leave us. So I think it's clear that contemporary regimens are much less likely to result in virologic failure and drug resistance.

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But that depends on regular monitoring of plasma viremia so that when treatment failure occurs it's identified and you can make the appropriate clinical decision either to intensify adherence counseling or to identify what is it about the regimen that's not working for that particular patient so that you can find a better regimen for the patient and switch them to something that they are more likely to take on a regular basis in order not to select for drug resistant resistance transmitted drug resistance is decreasing

in many countries like it throughout Europe but it's certainly on the increase in resource limited settings of where transmission not only of non-nucleoside or TN inhibitor resistance but also of tenofovir resistance because the case 65 are mutation is much more easily selected with subtype C viruses that predominate in sub-Saharan Africa is a big concern.

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On the other hand transmitted nucleoside resistance has minimal impact on the response to protease inhibitor or integrase inhibitor based based regimens and given the data that I've shown you and given that for the most part patients are now being started on integrase inhibitor based regimens it may really be time to re-evaluate just how much value are we getting out of doing a baseline drug resistance in those countries where it is now a standard of care and my colleague Paul Saks together with Ken Freiberg who did the initial cost effectiveness analysis demonstrating that it was worthwhile to do drug resistance testing are now reanalyzing their data with the sort of contemporary models using integrase inhibitors to see whether it still makes sense for us to have this recommendation because the data probably no longer support the necessity of doing pretreatment drug resistance testing if you're going to use either boosted API or an integrase inhibitor based regimen.

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So let me turn now to talk a little bit about resistance in PrEP very clearly prep regimens can select for resistance when PrEP fails and the big worry is that intermittent adherence could allow infection. Somebody has been on PrEP they stop PrEP they keep having sex and then they get infected and they go back to having PrEP and now they're taking what is really inadequate to drug therapy for HIV infection and that could select for drug resistance and then that could lead to the transmission of drug resistant virus because once you have this resistant virus that's no longer being adequately suppressed by your PrEP regimen you can transmit it to your next partner and clearly the the case that we saw earlier was an example of transmission of drug resistant virus. But there are factors that mitigate against the risk of of acquiring drug resistance in the context of PrEP. First of all there is a fitness cost for resistance mutations resistance only persists in the presence of drug for the most part. There's also a low prevalence of resistant virus in populations from untreated persons because we're not talking about people who are suffering. We're now talking really about the HIV infected people not on therapy. Some mutations like the one before the mutation actually enhance susceptibility to tenofovir so so long as we're using the combination of tenofovir an m tricitabine as PrEP if there is resistance to the m tricitabine of being component to actually the Tenofovir is made more effective and then high tissue concentrations as are achieved at least in the rectal mucosa may provide some additional pharmacologic barrier to the development of drug resistance.

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So if you look across all of the PrEP studies so these are all of Phase 3 trials of PrEP and look at the prevalence of resistance in those trials. What you can see is that the resistance is pretty low. Now what I

what I haven't done for you here is to show you the total number of people in the trials the end here refers to those who were actually diagnosed with HIV infection. So these are the PrEP failures and so in the iPrEx Study which was one of the less effective studies. A landmark study that certainly demonstrated efficacy but not earth shattering efficacy. There were 141 participants in the TDF FTC arm who became infected only three of them had resistance. All of them had evidence of resistance to the M tricitabine with either the 184 V or imutation and all of these were detected at the time of randomization. These are people who were sero negative but actually in retrospect were found to be either HIV positive or within a week or two of entering the study became RNA positive so they were infected at the time they enrolled into the trial got drug and then selected resistance for preexisting viral infection. The same is true in the partners PrEP study here in the US. There were three arms a placebo and then two drug arms a combination arm and a tenofovir arm. There were more infections although not significantly more than the TDF monotherapy prevention arm.

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You can see that there were for resistance for four of seven individuals who became infected in the dual arm had evidence of resistance to m tricitabine one of 19 in the TDF arm had a 65 R again all of these individuals were found retrospectively to have been infected at the time they enrolled in the trial. None of them acquired infection while on PrEP and then selected for for resistance in the TDF to study that was done by the CDC in Botswana. There were 10 people who became infected. A single person had evidence of resistance in this case resistance to both tenofovir and m tricitabine. But again this individual was infected at the time of enrollment but unrecognized because they were they were sero negative. And by contrast in the Bangkok tenofovir study there were 49 people who became infected none had resistance. And then in the FEM PrEP study which was actually a negative study overall it failed to demonstrate efficacy in this group of women given tenofovir FTC. There were 33 infections for had the 184 V or I. Three of these four were infected at the time of randomization. So here there was one participant who actually did become resistant while receiving PrEP infected and then became resistant. And in the VOICE study which was a 6 arm study that included tenofovir gel and oral tenofovir or tenofovir FTC and I'm only showing you the oral arms here together there were 140 people who became infected none in the TDF arm developed resistance for the combination arm developed resistance and again three of the four were infected at the time of enrollment into the study.

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So at least in this setting of clinical trials acquiring or developing resistance to PrEP when becoming infected because of PrEP failure is really extraordinarily uncommon and that is probably because nearly all PrEP failure is associated with failure to take PrEP and that was certainly the case in the in the PrEP and the VOICE studies so resistance in the emergence of drug resistance in PrEP is rare.

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It's most often found at the time of starting PrEP when somebody has unrecognized acute infection. It's much more common to have resistance to FTC and there are really only two examples so far of 65 R. Although Dr. Brassens case may be another example now and although I haven't shown you the data.

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Robert Grant and others have published data showing that in fact these mutations decay over time. And as we've learned in the setting of nevirapine resistance in mothers who receives single dose of nevirapine although resistance is selected quite readily. These resistance mutations don't become fixed in the population and persist in the reservoir unless the patients are on drugs for quite some time and so in the case of nevirapine six months later not only are the mutations undetectable but you it's harder to see a difference in terms of outcome. If you put people back on developing versus some other other therapy but if they are they still have resistance then it's obviously there's a bigger difference so what the clinical significance of once having developed 184 mutation on PrEP and then later going onto an integrase inhibitor regimen that includes tenofovir and FTC or 3 TC is really not yet clear. So to conclude a transmitted nucleoside and non-nucleoside resistance remains common in the U.S. but the impact of transmitted drug resistance on first line regimens has diminished as our first line regimens have become more and more potent and effective dolutegravir does select for integrase a resistance when given as monotherapy. It does not select for resistance as part of a combination regimen and nor does big tenofovir which has yet to be approved and resistance after PrEP failure seems to be really quite rare and hopefully can continue to be minimized by appropriate interval monitoring of people receiving PrEP to ensure that they have not become HIV infected in the interval. So let me stop there and I'll be happy to answer questions.

[Video End]