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XVII International AIDS Conference Late Break Track B Session 1 August 7, 2008

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JULIO MONTANER, M.D., F.R.C.P.C., F.C.C.P.: -and I will be firm in accepting questions that are thematic and are pertinent to the presentation. For any other demonstrations, I would appreciate that we wait until the sessions is over. Without further ado, we will pass it to Papa Salif Sow. The format of the session will be such that we will have 10 minutes for the presentations and five minutes for questions. Thank you.

PAPA SALIF SOW, Ph.D., M.D.: Thank you, Julio. Ladies and gentlemen, good afternoon. It is my pleasure now to introduce the first speaker, David Simpson from the United States, who will present us this communication on a randomized, double blind, placebo controlled, multicenter, trial of pregabalin versus placebo in the treatment of neuropathic pain associated with HIV neuropathy. David, you have the floor.

DAVID SIMPSON, M.D.: Thank you very much. And I would like to thank the chairs and the conference organizers for having the opportunity to lead this exciting session. I am going to discuss some very new data concerning management of painful peripheral neuropathy in HIV.

As background, over a third of patients with HIV and AIDS have neuropathy. In fact, recent data we have from an NIH study in the US says over 50-percent. Neuropathy is frequently misdiagnosed and under treated.

Of course, some of the medications used in HIV can cause neuropathy, such as the D drug antivirals. Pain is a major debilitating symptom. It affects quality of life, adherence to medication, and in several groups within the NIH, within neurology of HIV, neuropathy has been designated the single highest priority, and we focused on pregabalin because it has been demonstrated effective in several forms of neuropathy like diabetes, and post-herpetic neuralgia.

The primary objective of this particular study, 1066, was to evaluate the efficacy of pregabalin compared to placebo in reducing neuropathic pain associated with HIV neuropathy. There were a number of secondary aims, which I will come to through the course of the presentation.

These were male and female patients with HIV over 18 years old, 40 sites in the US and Puerto Rico participated. And the neuropathic pain needed to be present at least three months and confirmed by a neurologist on examination. Now this slide is a bit complex, but it summarizes the design of the study.

There was an initial screening period, patients were then randomized to pregabalin which is an anticonvulsant, the next generation of gabapentin which is a calcium channel agent working on the alpha 2-delta ligand of the calcium channel, and once patients were randomized, they either had placebo and they began at 150 milligrams per day.

Every four days they could then increase the dosage to 300 milligrams, and 600 milligrams based on tolerability. So this was a flexible dosing schedule where patients could increase dose based on how they tolerated the drug. They then had a 12 week maintenance phase of pregabalin versus placebo and then a wash out period.

Here are the demographics of the cohort. Placebo versus pregabalin. Approximately 150 patients in each group. About 80-percent of them were men, which although we would have like to have more women, this is better than most neuropathy studies have done in approving women.

In our cohort about 56 to 58-percent white, 38-percent black. And the history of D drug antiviral use. D4T and the others, 9 to 13-percent. Remember this was a US based cohort where D drug use is far less than it used to be, certainly not the same in other populations in other parts of the world. The mean pain score on a scale of 0 to 10, 0 being no pain, 10 being worst possible pain, was about 6.7 to 6.9. Moderate to severe pain.

As far as patients that discontinued the study, about 20-percent in both groups. Interestingly, most study discontinuations were unrelated to study drug. About 5-percent in the pregabalin group discontinued due to a drug related adverse event.

The dosing, remember patients could dose from 150 milligrams to 600 milligrams per day, and the average daily

dose in the pregabalin group turned out to be 386 milligrams. And here you see the breakdown of the three dose groups in the pregabalin group. About 53-percent were able to get to the maximum dosage of 600 milligrams.

So here is the first primary result. Remember that it was a 14 week trial and this is pain reduction from 0 to 10. Patients began with a median of 6.7 in pain and here we have the absolute reduction. Pregabalin in blue. Placebo in yellow.

Notice that at Week 1 and Week 2 there was a significant difference in pain reduction favoring pregabalin although the placebo response then almost met the pregabalin response, and there was no further significant difference from Week 4 and beyond.

Here is another way of demonstrating the data result. This is the so called 50-percent response rate. This is the percentage of patients that had at least a 50-percent reduction in their pain from baseline. And although the absolute reduction was good, about 40-percent of patients had a greater than 50-percent pain reduction, no difference between pregabalin and placebo.

Another of the secondary outcome measures was the patient global impression of change. How did patients feel about how they did in the study? From worse, no change, to improved. And notice here that there now was a difference favoring the pregabalin group in this global patient measure.

As far as adverse effects, if we compare pregabalin to placebo, we see the similar types of effects observed in other studies for pregabalin and neuropathy. Somnolence, dizziness, euphoria, and peripheral edema being most common.

And so the conclusions of this first pass of the data is that there was no difference in end point mean pain score between pregabalin and placebo. Although up to Week 2 pregabalin was favored, it did not extend beyond Week 2. And responder rates also did not differ. I did not show you sleep interference score, which is the amount that pain interfered with patients' sleep and this favored pregabalin up to Week 6, but not beyond Week 6.

And we have talked about the global measure result. As far as safety, the safety results were very similar to those seen in studies of diabetic and post-herpetic neuralgia with a relatively low rate of discontinuation.

Now, to conclude to put these data into a bit of context, I have already mentioned that pregabalin has been demonstrated effective in other forms of neuropathy, particularly diabetic and post-herpetic neuralgia and why do we see a different result here with lack of efficacy as compared to those other responses?

Well here is a bit of a representative meta analysis. This is our current study that I presented today in HIV neuropathy. Here we see five pooled studies of pregabalin in post-herpetic neuralgia, and now we see seven pooled studies of

pregabalin in painful diabetic neuropathy. And here we have placebo, and several doses of pregabalin.

Notice that in the successful studies in PHN and diabetes, the placebo response was far lower than we saw in the current trial, whereas the active pregabalin response in fact was quite comparable across these studies. So it was the higher placebo response in this study that washed out the effectiveness.

Now, I cannot possibly do justice to putting this study in context of all other studies done in symptomatic painful HIV neuropathy. This single slide boils down a lot of trials to the single primary outcome. All placebo controlled studies in HIV neuropathy.

Notice many things did not work. Amitriptyline, which is a tricyclic antidepressant, acupuncture versus sham acupuncture, mexiletine, a type of lidocaine, lidocaine gel. Notice that several of the anticonvulsants, lamotrigine and gabapentin did show some improvement although these were very small and difficult to replicate results. We did have some very exciting data with the high concentration capsaicin patch that we published in *Neurology* just a couple of months ago.

Unfortunately, the first Phase III positive result was not replicated in a second similar design. And one intriguing study from San Francisco showing smoked cannabis showed pain improvement. We now have several studies that are on the horizon that are soon to open, combinations of duloxetine, a

type of antidepressant with methadone, and a cannabinoid and methadone.

There are numerous articles discussing why neuropathic pain is difficult to treat. And this couple of papers indicate for instance it is unclear whether these trials were unsuccessful because the medications truly lack efficacy or whether the characteristics of the trials compromise the demonstration of treatment benefit.

And finally my last slide, although this is virtually impossible to read, this acknowledges the 40 sites that were participants and the support provided by Pfizer in conducting the trial. Thank you very much. [Applause.]

PAPA SALIF SOW, Ph.D., M.D.: Thank you, David. Now this paper is open for questions. We have time for three questions. Yes, go ahead.

MALE SPEAKER: Coboda from the United States. Was there any duration of diagnosis? Did that make a difference in the response rates?

DAVID SIMPSON, M.D.: The duration issue in the demographic slide I went through this very quickly. But the duration of neuropathy was on the order of approximately six or seven years. But as far as a subanalysis of whether duration of neuropathy had any impact on response, we have not yet done that type of analysis. These are very recent data, and those types of secondary subanalyses, in a sense post hoc, will follow in the future.

PAPA SALIF SOW, PH.D., M.D.: Yes, next question? So, David I have a question. To which clinical stage were these HIV patients when they were put on this new drug?

DAVID SIMPSON, M.D.: At which clinical stage? In terms of HIV and their disease state?

PAPA SALIF SOW, Ph.D., M.D.: Absolutely, yes.

DAVID SIMPSON, M.D.: I do not know that I can answer that question specifically. I am not sure if it is possible to pull up the demographic slide again. But we do have the CD4 counts for these patients which would perhaps answer that question. By memory I believe that they ranged somewhere in the 300 or so range, but I would have to go back and look at that.

PAPA SALIF SOW, Ph.D., M.D.: Okay.

DAVID SIMPSON, M.D.: One point that can be made, let me see if we can pull that up. Here is duration. No, I am sorry. We do not have the CD4 information up here. But one of the points that I would comment on is that when we look at our database of neuropathy in at least US based studies today, it turns out that these are not all advanced patients. The pre-HAART type of patient with very low CD4 being the most likely to have neuropathy is no longer the case. We now see quite a bit of neuropathy in patients who have relatively good CD4 counts, whether immune-reconstituted or otherwise.

PAPA SALIF SOW, Ph.D., M.D.: Thank you. Last question?

MALE SPEAKER: Any thoughts on why your placebo patients responded so well compared to previous placebo trials?

DAVID SIMPSON, M.D.: Well that is the big question. Why such a high placebo response? The short answer is I do not know. There does appear to be in the HIV field, particularly this very unpredictable placebo response in neuropathy trials.

And as an example, in the high concentration capsaicin studies that I referred to earlier, the active response in the first and the second trial was almost exactly the same, but the placebo response in the two trials was quite different, leading to a first successful response, and the second showing no difference from placebo. But why that is remains purely speculation.

PAPA SALIF SOW, Ph.D., M.D.: Thank you very much, David for this paper. [Applause.] Now we are moving on to the next one, the 302, which will be presented by Joseph Babigumira from United States on the cost effectiveness of programmatic models for provision of antiretroviral therapy in resource limited settings. Joseph, you have the floor.

JOSEPH BABIGUMIRA: Thank you very much. I am very privileged to present this study on behalf of my co-authors, Dr. Sethy [misspelled?] from the University of Madison in Wisconsin, and Drs. Smith and Singar [misspelled?] from Case [misspelled?] in Cleveland, Ohio.

This was a cost effectiveness study of programmatic models for the provision of ART in resource limited settings.

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The current scale up on future sustainability of ART programs in poor countries is limited, as we all know by our resource scarcity.

And this scarcity implies that we have to make very tough choices with regard to the allocation of resources, especially personnel and drugs and infrastructure. And currently ART programs are rolled out in a variety of ways, and there has been little attempts at formal efficiency evaluations. So this study was an attempt to contribute to the efficiency frontier in the policy discussion, which we feel is an important aspect of the policy agenda.

The objective of the study was to compare the cost effectiveness of different programmatic models for provision of ART in resource limited settings, and we used the example of rural Uganda.

So what did we compare? We compared facility based care where patients are responsible for transporting themselves to clinic sites with mobile clinic care where patients sort of have the distance from their homes cut short by having mobile clinics taken a little bit closer to their homes, and with the well studied home based care, where all care takes place in patients' homes.

And working under a hypothesis that access is not best in facility based care. It improves with mobile clinic care, and is highest for home based care. And this was also a similar hypothesis for adherence to antiretroviral therapy.

So we did a decision analytic mark up model, and we followed the hypothetical cohort of rural 35 year old Ugandans, and they were all in Stage 3 and 4 of disease. The model was based on clinical stage. We did a prospective of the Ministry of Health and of course excluded non-provider costs.

The data came from primary surveys as well as the published literature. The time horizon was ten years, and the main outcomes were cost, life expectancy, incremental cost effectiveness as measured by cost for quality adjusted life year, and the cost and outcomes were discounted at 3-percent, and used a willingness to pay or cost effectiveness threshold of between 1 and 3 times the gross domestic product.

Of course in Africa it would vary, but for Uganda it would be between \$350 and \$1,050. And we did probability sensitivity analysis using [inaudible] simulation.

So this was the decision tree. As you can see patients enter the model when they are eligible for HAART and they go to one of three programmatic models. If they access HAART then they will go to the upper branch. If they do not, then they go to the lower branch.

And then we have a branch for adherence or non-adherence. And this transitions into a mark up model and our mark up model had seven states, and the cycle time was six months. And for each cycle patients are allowed to transition as follows: To move between Stage 3 and 4, to remain adherent,

to become non-adherence, or to die. Or sorry, to remain non-adherent as well.

And these are the data that we used to populate the model. These are the six month transition probabilities taken from the literature. As you can see, in Stage 3 and 4 the rates of transition as well as the mortality. I will not go through them one by one because of time.

And then these are the access assumptions and data. The access to ARV in Uganda in general in 33-percent. And adherence for home based care was the highest with 85-percent adherence.

And then we performed a primary health related quality of life survey. The instrument was FU5B, and these are the results of that survey. These are utilities, and for non-ART patients it is 0.69 and for ART patients it is 0.84 in Stage 3. And in Stage 4 the utilities are lower for non-ART patients as well as for ART, but they presented quite good quality of life.

And these were the costs. For the first year of home based care, it costs \$1,000 per patient per year. And then those were the overhead costs for the different programmatic models.

For home based care, \$600, facility based care, \$229 and mobile clinics, \$502. \$237.50 was the cost of ART drugs and the cost of illness in both stages refers to all non-drug costs of managing patients. And all costs are in 2008 US dollars, that done using a South Africa consumer price index.

So this is really the result of the analysis. As you can see, the expected survival at ten years for facility based care would be 9-percent. For mobile clinics it would be 13-percent. And for home based care, it would be 21-percent. I also call your attention to the costs for home based care being \$6,000.

For facility based care being almost half that. And then I also draw your attention to the figures in red, the incremental cost effectiveness ratios. And these differ from the data in the abstract primarily because cost assumptions have since improved.

The ISA in cost per life years was 15 for mobile clinic care and 24.32 for home based care. And in terms of quality adjusted life years, it was \$224.51 per quality adjusted life year, and \$28.93 per quality adjusted life year for home based care.

And I also put there the threshold just so you know what kind of willingness to pay we used as our threshold assumption.

One [inaudible] sensitivity analysis indicated that this model was sensitive to the overhead cost of facility based care as well as home based care, and our mobile clinic model always got eliminated by extended [inaudible] that meaning that different combinations of home based care and facility based care make mobile clinic care not cost effective. The model was also sensitive to high levels of access to facility based care

and home based care. And low levels of adherence and access to mobile clinics. And again, mobile clinics were eliminated by extended [inaudible]. For all other variables, the model was quite robust.

And this is the results of our probability sensitivity analysis. As you can see, this is a point where all models have the same percentage cost effective, and you see that the willingness to pay is right down here, very low about \$300 US and if you take the upper part of three times the GDP it goes to right there. And it shows that for facility based care, it is highly cost effective with a high percentage. And home based care becomes cost effective at high values of willingness to pay.

So our study had some limitations. And we had not the best quality of access and adherence data. And also we do not really know in the data, in the literature what happens when patients stay on HAART for a long time. We know that in Africa adherence is really good, but we do not know what will happen in the next 15 years when the patients have been on drugs for a long time. And we also did not have a resistance parameter in this model, and we feel this is an important limitation to point out.

So in conclusion, facility based care was the most cost-effective programmatic model for ART provision, and this analysis supports that this should be the way to scale up and sustain ART programs in the long term. Especially given that

our levels of constrained maximization are really, really severe.

Because we have very low budget constraints, with most countries having three or four dollars of per capita health expenditure. And other care models really would need to demonstrate superior levels of access and adherence or largely reduced costs to become competitive.

And we also see that home based care would be really cost effective if the willingness to pay was high. So if the threshold was \$5,000 then that would be a different story, but in the face of such severe budget constraints like I said, most countries spend very, very limited amounts of money per capita on health, we feel that such a scenario would be very, very remote.

I would like to acknowledge funding from the NIH and the Fogarty International Center, and the International Clinical and Operation on Health Sciences Training [inaudible] Care System as well as the Rakai Health Sciences Project and Uganda Cares, as well as Bry [misspelled?] University and McKay University who are our partners in this project. Thank you.
[Applause.]

PAPA SALIF SOW, Ph.D., M.D.: Thank you, Joseph for this communication. Now this paper is open for questions. Do we have questions for Joseph? Joseph, did your model include as costs for the drug for the treatment of opportunistic infections?

JOSEPH BABIGUMIRA: Yes, that is a good question. And that is included in the cost of [inaudible] for Stage 3 and 4. So those costs were there.

PAPA SALIF SOW, Ph.D., M.D.: Okay.

MALE SPEAKER: Two questions. The first one is I suspect that you did not include the cost of building the facility. If you did that, the facility based care would be equally competitive?

Joseph: We did not have those costs. I believe that most of the infrastructure exists, but I think that would probably drive facility based care to become a little bit less cost effective.

MALE SPEAKER: The other thing is in your mobile model, would it change the equation if you used different types of mobile, so I do not know exactly what the model looked like, but if you used cars or ambulances, or trucks or bicycles. Is the means of transportation driving the cost? Is the personnel?

JOSEPH BABIGUMIRA: I think the key cost driver would be transportation. And remember these prospective was the ministry of health, and that implies that you forget about what the patient pays. But then if the Ministry of Health pays for transport to people's homes, that is what causes home based care to be expensive. And we have not done the first time costs for vehicle and for infrastructure, and our working assumption is that those would be already in existence.

PAPA SALIF SOW, Ph.D., M.D.: Thank you. We have two questions there.

MALE SPEAKER: Thank you for that nice presentation. I am just wondering if you have thought a little bit in following through on Julio's question about the one, the fixed costs that are associated with facilities, that is infrastructure, which is usually quite great, and one would have to actually have to have ongoing maintenance costs to go into that, and factoring that in.

And then with the home based or mobile care, what are the array of levels of proficiency that you need? For instance, in Haiti they have unskilled outreach workers who do the amount of work which is relatively inexpensive, versus having physicians go out there, and so what would be the level of skills, and have you looked at various models in the home based care and factored it into your cost effectiveness analysis?

JOSEPH BABIGUMIRA: Those are all very, very good questions, and your points are well taken. I would say, though that first of all our working assumption, especially from Uganda is that infrastructure would present, and really the health centers exist.

And that all overhead costs would be taken care of. Now that is not always the case, but it was our working assumption. With regard to personnel, some data from our group indicates that task shifting has a very, very positive economic

impact. And that would be a good addition to the model and it is a point well taken.

MALE SPEAKER: Thank you very much.

PAPA SALIF SOW, Ph.D., M.D.: Next, could you please identify yourself?

SYLVIA GILLENITE: Yes. Sylvia Gillenite [misspelled?] from Vancouver, Canada. I wanted to ask you if there was a chance for patients that went in one type of model for example, in the home based model, to switch to the facility level model, meaning that once they were more stabilized and they were identified by the health care system, if you can switch patients from one model to the other. Did you explore that possibility?

JOSEPH BABIGUMIRA: I did not quite get your question, but if I got it correctly, we really assumed that in our cohort once when you were directed into one model, then you did not have a chance to switch. But obviously in real life it would be impractical. People could switch.

And I would like also to emphasize that really we are not trying to say that home based care is bad, but we are just contributing to the policy discussion and seeing the body of evidence on home based care to demonstrate cost effectiveness.

PAPA SALIF SOW, Ph.D., M.D.: Okay, the last one.

SAM RUTHERFORD: Sam Rutherford [misspelled?] from Simon Fraser University. In optimizing delivery of health care operations, scheduling theory is used a lot, at least in

the West. But that is a lot easier to do with facility based care versus home based care. Did you look? Was that part of your calculation?

JOSEPH BABIGUMIRA: That was not part of our calculation. And that is also a point well taken. But obviously in a modeling framework, the complexity, there is limitations with how much you can model, but that is a point well taken.

PAPA SALIF SOW, Ph.D., M.D.: Thank you, Joseph for this paper. [Applause.] Now we are moving to the next one, the Paper 303, the ACTG 5202: Shorter Time to Virologic Failure with Abacavir/Lamivudine than Tenofovir/FTC as Part of the Combination Therapy in Treatment Naïve Subjects with Screening with HIV RNA more than 10,000 copies per mL. Paul, you have the floor.

PAUL SAX, M.D.: On behalf of the ACTG 5202 team, I would like to thank the organizers for allowing us to present these data, the ACTG 5202 which compared abacavir/3TC and tenofovir/FTC in patients with screening HIV RNA greater than 100,000 copies. As you know, abacavir/3TC and tenofovir/FTC are recommended NRTIs in multiple guidelines for initial therapy. Our hypothesis related to the NRTIs was that abacavir/3TC was equivalent to tenofovir/FTC when combined with ethavrins [misspelled?] or atazanavir.

This is our study design. 1,858 patients were enrolled and then randomized to one of four treatment strategies. For

the nucleoside component they received tenofovir/FTC plus abacavir/placebo or the received abacavir/3TC plus tenofovir/placebo. And then the third drug was either ethavrins or ritonavir boosted atazanavir. The nucleoside component of the study was blinded, and patients were stratified upon entry to have less than or greater than 100,000 copies of HIV RNA.

The study began in September of 2005 and completed enrollment in November of 2007. We planned 96 weeks of follow up after the last subject was enrolled. And the study completion therefore is anticipated in the fall of 2009.

We have three primary end points. The first end point is an efficacy end point which is a time to virologic failure end point. Early virologic failure was defined as a confirmed HIV RNA greater than 1,000 copies between weeks 16 and 24. Later virologic failure was a confirmed HIV RNA greater than 200 copies from Weeks 24 on.

This could be either failure to achieve a viral load less than 200, or achieving it and then rebounding. The safety end point was time to the first Grade 3 or 4 sign, symptom, or lab abnormality, at least one grade higher than baseline. And tolerability was the time to modification of the initially randomized regimen.

In January of 2008 the data safety monitoring board met to review the study for efficacy for the first time, and they found excess virologic failures with abacavir/3TC. The DSMB

requested that the four arms be combined into two and we do an analysis comparing abacavir/3TC versus tenofovir/FTC.

The findings of this analysis showed highly significant differences between abacavir/3TC and tenofovir/FTC with excess virologic failures on the abacavir/3TC arm occurring the greater than 100,000 copy stratum. They then recommended that we unblind this stratum and that is the results you will be hearing today.

Only the results from this stratum and only the comparison between abacavir/3TC and tenofovir/FTC. This included 797 study subjects with a median follow up of 60 weeks. There was a low rate of study drop out or loss to study, and did not differ between arms.

The baseline characteristics of the study are shown here. Overall the study subjects were well matched. They average 39 years of age, 85-percent were men, the baseline HIV RNA was 5.1 log. And the baseline CD4 cell count was 181 cells. Genotype was required at screening only if patients had recently acquired HIV infection within the past 12 months.

However, it was done at some study sites as standard of care at the time. So overall, 43-percent of study subjects did have genotype testing done at baseline before they entered the study. If patients had resistance mutations as defined by the IAS USA list, then they were excluded from the study.

And here is the primary end point which is time to virologic failure. As you can see there were 57 events in the

abacavir arm and 26 events in the tenofovir/FTC arm. And this was highly statistically significant with a P value of 0.03 and a hazard ratio for failure of 2.33.

This, I just want to orient you. Red is the abacavir. Blue is the tenofovir. And along the horizontal axis are time in weeks, and along the vertical axis is the proportion remaining free of virologic failure.

This slide looks at the timing and type of virologic failure that occurred in the study. Once again, there were 57 virologic failures in the abacavir/3TC arm and 26 in the tenofovir/FTC arm, and you can see that there is a consistent excess of failures in the abacavir/3TC arm regardless of the criterion we used for virologic failure.

Either early failure as shown here, or later failure without achieving less than 200, or later failure after achieving 200. We did conduct a post hoc analysis looking at patients who achieved viral loads below 50 copies at least twice. In this analysis virologic rebound was infrequent in both arms, and did not differ significantly between tenofovir/FTC and abacavir/3TC.

This next analysis looks at the time to regimen completion, which would be the first occurrence of either virologic failure or nucleoside modification. There were 114 such events for abacavir/3TC and 68 events in tenofovir/FTC for a P value of less than 0.01. Nucleoside modifications occurred in 95 abacavir/3TC patients and 52 tenofovir/FTC patients.

In 5202 we allowed patients who experienced virologic failure or nucleoside modification to remain in the study, and we were able therefore to look at outcomes not just of our first regimens, but also of subsequent regimens. In this analysis, we look at the proportion of patients who are below 50 copies at various time points allowing for regimen changes and prior virologic failure.

At Week 48, 75-percent of the abacavir/3TC arm and 80-percent of the tenofovir/FTC arm had viral loads less than 50 copies for a P value of 0.20. This describes the CD4 cell count change. And as you can see there is no difference between study arms. Study subjects started with a median CD4 cell count in the high one hundreds, and at the end of this observation period, were over 400 in both arms.

Now moving on to safety, the time to the first safety event, which was safety remember was defined as Grade 3 or 4 sign or symptom or a lab abnormality one grade higher than baseline. There were 130 events for abacavir/3TC and 78 events for tenofovir/FTC for a P value of less than 001. Hazard ratio is 1.89.

When we look at these safety events as shown in the next table, I want to emphasize few things. These are some of the events that occurred in more than 5-percent of the patient population. A lot of this is comprised of metabolic affects, meaning changes in lipids, and these changes in lipids that occurred between the two arms were generally small in

magnitude, and I think unlikely to be clinically significant. In addition, there were quite a few non-specific aches and pains and other things that accounted for this difference.

There were targeted events that we are interested in. They were protocol defined and reported by the study sites. These included fractures, myocardial infarction, malignancy, renal failure, suspected HSR, and deaths.

And as you can see there were low numbers of these events in both arms, notably no myocardial infarctions in either arm, and two cases of renal failure in both arms. There was one subject in the abacavir/3TC arm who died possibly due to drug hypersensitivity reaction, after re-challenge.

So to conclude, in patients with screening HIV RNA greater than 100,000 copies per mL, abacavir/3TC was associated with a significantly shorter time to virologic failure than tenofovir/FTC. There was no obvious relationship between suspected HSR and virologic failure. In addition, abacavir/3TC had a shorter time to the first adverse event.

The resistance analysis including baseline and with failure, as well as numerous other analyses related to this population are currently ongoing and I want to say also that the remainder of ACTG5202 continues until November 2009. And this includes the blinded nucleosides in the lower viral load stratum, as well as ethavrins versus atazanavir.

My last slide really discusses why the results of 5202 might differ from other studies. Now it goes without saying

that study follow up, design, end points, and conduct clearly differ between studies, and we will hear more about that shortly.

But if you look only at the studies that directly compare abacavir/3TC and tenofovir/FTC, that is 5202 and HEAT, two things stand out. One is that the sample size in 5202 is substantially larger, and this larger sample size may have allowed us to describe differences between the groups with greater precision than with a smaller sample size.

And the second is that our study used a different third drug, either atazanavir, etonovir, or ethavrins, versus lopinavir or etonovir capsules [misspelled?] in HEAT. I will also say that there are other studies of course looking at abacavir/3TC in various prospective trials, but they did not compare the similar nucleoside strategies.

I would like to finish by thanking my protocol co-chair, Eric Darr [misspelled?], my vice chairs, Anne Collier and Margaret Fischel [misspelled?], and our chief statistician, Cameron Tierney [misspelled?].

There was also a large group of protocol members who are listed here, and thanks also to our industry collaborators from Abbott, Bristol Myers Squibb, Gilead Sciences, and GlaxoSmithKline. And thanks especially to the numerous ACTG sites and the patients who volunteered to be in the study. Thank you for your attention. [Applause.]

PAPA SALIF SOW, Ph.D., M.D.: Thank you, Paul. Thank you, Paul for this communication. Now this paper is open for questions. Yes, Microphone Number 1.

FEMALE SPEAKER: Paul, can you tell us how many people stopped therapy because of virologic failure? Because at the end of your discussion, the numbers less than 50 are similar.

PAUL SAX, M.D.: So after patients experienced virologic failure, they were allowed to either remain on their original nucleosides, or modified nucleosides depending on the results of resistance testing. So-

FEMALE SPEAKER: So do you know how many-?

PAUL SAX, M.D.: I do not have that number off the top of my head, but once virologic failure occurred, management of those patients was according to sort of standard of care at the site and could include for example, if patients had no resistance at all, continuing the same regimen with redoubled interest in adherence.

PAPA SALIF SOW, Ph.D., M.D.: Microphone 2.

ANNAMARIE VENSING: If you consider-

PAPA SALIF SOW, Ph.D., M.D.: Could you please identify yourself?

ANNAMARIE VENSING: I am sorry. Annamarie Vensing [misspelled?], in [inaudible]. If you consider that transmitted resistance is about 10-percent and mainly that will be [inaudible] mutations, can you think that this could be the

reason that people started on abacavir did less well? Because abacavir regimens might be more affected by that?

PAUL SAX, M.D.: So the question is about transmitted resistance. So, as I mentioned, 43-percent of the study subjects did have genotypes and they were excluded if they had resistance. And since we do not have resistance data the other group yet, we did do a sensitivity analysis looking at whether a patient had a genotype or did not have a genotype, change the outcome in any way, and based on that analysis it did not.

PAPA SALIF SOW, Ph.D., M.D.: Microphone Number 1.

MALE SPEAKER: Boling. Los Angeles. I noticed that the abacavir arm had significantly greater adverse events, and I wondered did you do any other measures of adherence, so is it possible that the people that had greater adverse events in the abacavir arm just did not take their meds and this could be responsible?

PAUL SAX, M.D.: So, the question about adherence and whether it influences outcome. It is possible, and one of the analyses that we plan to do is reported adherence.

PAPA SALIF SOW, Ph.D., M.D.: Microphone Number 2.

JOSE SARATEL: Jose Saratel [misspelled?] from Barcelona, Spain. The question is related of whether the difference can be explained for those patients who did not reach a detectable viral load before Week 24? Because in the stratum of the patients with more than 100,000 copies, not all antiretroviral regimens may be equally fast to reach detectable

values and then later on they can achieve the same rate, and this is what we have seen for example in the [inaudible] studies.

PAUL SAX, M.D.: Well all of the protocol chairs have to sign off on the virologic failures. And I can tell you just looking at those, only a very small proportion if any I can remember would have met that reason for virologic failure as you have described, meaning people who are still on their way down and still are called virologic failure. But that is a specific question that we will look into further.

PAPA SALIF SOW, Ph.D., M.D.: The last question.

MARSHAL DeSOUZA: I am Dr. Marshal DeSouza [misspelled?] from Fort Myers, Florida, United States. I am surprised that in both the arms the hypersensitivity reaction was similar. My first question is what kind of criteria was used? And the second question is what was the third regimen? Was it the Favirin [misspelled?] or was it the ATV and the ritonavir?

PAUL SAX, M.D.: So, sites were extensively educated about recognition and management of suspected hypersensitivity before the study began, because obviously in a blinded study we want people to be very cautious about this issue. What we noted in this study which has been seen in previous studies, especially studies that include ethavrins, is that the rate of miscalls or overcalls on HSR is significantly high.

So it has not been uncommon in other studies to have similar rates of HSR in blinded studies. The second question was related to the third study drug. And the DSMB has not released to us the data involving the third drug either for toxicity or for efficacy.

PAPA SALIF SOW, Ph.D., M.D.: Thank you, Paul.

[Applause.] Now it is my pleasure to give the floor to my co-chair, Julio.

JULIO MONTANER, M.D., F.R.C.P.C., F.C.C.P.: Thank you very much. The next paper is going to be presented by Keith Pappa and it is entitled abacavir/Lamivudine Shows Robust Virologic Responses in ART-Naïve Patients for Baseline Viral Loads of over 100,000 and less than 100,000 by Endpoint Used in ACTG5202, by Pappa, Hernandez, Ha, Shafer, Brothers, and Lao [misspelled?].

KEITH PAPPA: I would like to thank the organizers for the opportunity to present on behalf of my co-authors, Hernandez, Ha, Shafer, Brothers, and Lao. [inaudible] virologic response data in ART naïve patients with baseline viral loads above and below 100,000 copies using the ACTG 5202 end point. The A5202 study compares an Epzicom and Truvada backbone with either ethavrins or boosted atazanavir.

As just presented by Dr. Sax, the A5202 end points are unique. The interim results are unexpected in that we have not seen data suggesting Epzicom is less potent in patients with high viral load. The data is not consistent with prior

clinical experience, and raised the question of whether the two nucleoside backbones have comparable efficacy and safety.

Because of these points, when GSK became aware of these data from 5202, we undertook an evaluation of data from six recent trials using the 5202 end points. And now we include 96 week data from HEAT, a fully powered, double blind, randomized trial comparing Epzicom with Truvada with lopinavir/ritonavir.

In my presentation, I will address the question of whether avacavir/3TC is really less effective in patients with viral loads greater than or equal to 100,000 copies. I will review data from six trials utilizing the 5202 end point. And I will review the 96 week HEAT data.

I will also address whether abacavir/3TC is really less tolerable than tenofovir/3TC utilizing HEAT data including the A5202 safety end point, adverse experiences leading to discontinuations, and lipid changes utilizing the NCEP guidelines.

As you have heard, the primary efficacy end point in 5202 was time to virologic failure using Kaplan-Meier methodology. This was defined as confirmed viral load greater than or equal to 1,000 copies at or after Week 16 and before 24 weeks or greater than or equal to 200 copies at or after 24 weeks. The 1,000 copy cutoff and the use of Week 16 criteria is what is unique in this study.

Epzicom is a well studied compound with a variety of third agents. We analyzed six recent clinical studies which

utilized an abacavir/3TC backbone with a non-nucleoside and with boosted PIs. The studies highlighted in yellow utilized similar regimens to that used in 5202. These trials were conducted under good clinical practice standards. They were monitored, audited, and some included as registrational trials so that they are at the highest standard of conduct.

This slide presents the Kaplan-Meier estimate of probability of virologic survival by Week 48, by baseline, using the A5202 end point for five of the trials just described. Along the Y axis is percent of virologic survival. And across the X axis are the titles of the respective trials along with their sample size.

The red bar is low viral load stratum. The green bar is greater than or equal to 100,000 copies. You can see that there are no appreciable differences between the low and high viral load data in a total of 2,940 treatment naïve patients. The range of response in all six studies is between 87 and 95-percent.

As in the previous slide, this is the same end point, probability of protocol defined virologic survival by Week 48, by viral load, using the A5202 efficacy end point. The orange bar represents the Epzicom treatment and the blue bar is Truvada.

Again, this is from the HEAT study. The left bars are the low viral load stratum, and the right bars are the greater than or equal to 100,000 copies. As was the case for the five

clinical studies on the prior slide, the outcomes in the HEAT study are also very similar for the low and high viral load patients.

This slide presents primary and secondary efficacy end point data for the fully powered HEAT study. The 95-percent confidence intervals are shown across the top. This portrays the RNA less than 50 copies at Week 96. For more details, Dr. Kim Smith has Late Breaker Poster 1138 and it is being presented now in Hall D, Level 2.

As reviewed, the missing equal failed data at Week 48 was 68 and 67-percent as presented at the retrovirus conference. These data form the basis for conclusion of non-inferiority between Epzicom and Truvada in the HEAT trial and the result is consistent across the various end points.

Regarding efficacy, summary data from six recent trials using the A5202 end points indicates consistency in efficacy between low and high viral load data. The HEAT 96 week data confirm non-inferiority of avacavir/3TC with tenofovir/FTC.

The primary safety end point in 5202 was defined as time to development of first Grade 3 or 4 sign, symptom, or lab abnormality that is at least one grade higher than at baseline. CK and bilirubin values were excluded, and as Dr. Sax indicated, HLAB5701 testing was not the standard of care at study initiation.

So it was not part of this study. We saw similar results for the safety end point in the five clinical studies

just reviewed. Since the HEAT trial compares Epzicom with the Truvada backbone directly, we present the results for the 5202 end point in the HEAT study on this slide.

These are the specific events that are Grade 3 or 4 sign, symptom, or lab abnormality greater than or equal to one grade higher than baseline for patients with baseline viral loads greater than or equal to 100,000 copies per mL. You can see the frequency of events is low and comparable between treatment groups.

The true test of regimen tolerability is measuring study discontinuation. Here are the specific events in two or more subjects with baseline viral loads greater than or equal to 100,000 copies from the HEAT trial at Week 96. From the table you can see the events occurred very infrequently and were comparable between treatment arms.

This slide presents fasting lipid changes from baseline to week 96 for subjects with baseline Viral loads greater than or equal or 100,000 copies using the NSEP cut-offs in the HEAT trial.

The pink bars indicate NSEP cut-offs. Notable are similar increases in triglyceride for both Epzicom and Truvada at week 96 and increases in beneficial HDL cholesterol for both Epzicom and Truvada. Not shown on this slide is data indicating a favorable total cholesterol to HDL ratio at week 96 for both Epzicom and Truvada arms.

Regarding safety data, the HEAT data utilizing the 5202 endpoints as well as typical safety end points indicate both Abacavir 3TC and tenofovir FTC regimens are well-tolerated, have comparable safety, as well as few study discontinuations due to adverse experiences.

The reason 5202 findings are unexpected. They differ from clinical experience and they utilize primary efficacy and safety end points which are unique. Utilizing the 5202 endpoints analysis of six recent clinical studies using Abacavir 3TC demonstrate robust results, irrespective of baseline Viral loads. And according to the data just reviewed, Epzicom is effective in patients with high Viral loads.

The 96-week data confirmed non-inferiority of Epzicom with Truvada. Both regimens are well-tolerated, comparable safety and few A-list study leading to discontinuations. I would also like to mention Late Breaker information as is presented in Dr. Smith's posture. There is with no increase in CRP and IL6 from baseline to read 48 and 96 with Abacavir 3TC or tenofovir FTC in the HEAT trial. There were no significant differences between the treatment groups and I refer you to the posture for further information.

We, as part of the 5202 study team, look forward to further data regarding the impact of baseline resistance, treatment interruptions, adherence data, lipid changes using the NSEF guidelines, stratifying by screening Viral Load using local labs as well as differences in endpoints.

I would like to acknowledge, especially thank all participating study subjects, site personnel and study teams. Thank you.

PAPA SALIF SOW, Ph.D., M.D.: We have time for few questions. Identify yourself please.

GULLICK: Gullick [misspelled?] from New York. Keith, thanks for that presentation. One of the ways that we evaluate clinical trials when we try to apply them to clinical care is how generalizable the results are to the patients that we take care of. We heard from Paul Sax that 5202 had representation from 15 percent women and over half of the participants were people of color, either African-American or Latino. Could you give us a sense of the gender and race ethnic breakdown of the studies that you just reviewed for us?

KEITH PAPPA: I do not have the specific numbers strip. That is a great question. I would say that they do provide broad representation. I cannot tell you that they are exactly the same numbers as in 5202.

PAPA SALIF SOW, Ph.D., M.D.: Can we take a question from the other microphone?

EMMANUEL LEHOUX: Emmanuel Lehoux [misspelled?] from Sydney. Is it possible that ACTG5202 being so much larger was able to pick up a smaller difference which would have fallen outside your non-inferiority assumptions in HEAT but would still be a clinically-relevant difference for prescribing finished clinicians?

KEITH PAPPA: Can you restate that again, please?

EMMANUEL LEHOUX: Well, the ACTG study is much larger than HEAT so it would be able to pick up smaller differences which may be falling outside the statistical assumptions for the HEAT study. These differences may not be seen in HEAT but seen in ACTG5202 and be relevant for prescribing clinicians?

KEITH PAPPA: By understanding of the power is that it allows one to perform an analysis with greater precision, not necessarily to pick up larger differences. The HEAT study is fully powered at 90 percent power for non-inferiority and that is what it had showed. Epzicom is non-inferior to Truvada.

PAPA SALIF SOW, Ph.D., M.D.: I would take two more questions, one from Joe and another one from the other microphone.

JOE ERRAN: Yes, hi. Joe Erran [misspelled?], from Chapel Health. One, I just like to state that whether one study is more real than the other is a matter of debate and I think the way you introduced your presentation that you were going to show up was really true is a little bit, I do not know, disingenuous.

So, my question for you is it looked like in each of the six studies that you showed that the success at the lower Viral load was actually greater than at a higher Viral load. So if you actually did a cumulative analysis across all six studies, which is your significant difference between Avacavir 3TC at a lower Viral load versus a higher Viral load.

KEITH PAPPA: That is a great question. Thanks, Joe. I think it is important certainly to note that cross study comparisons are difficult. These trials were different as far as entry criteria and so forth. I think that really what we have is to look at the consistency of response and the percentage point difference; I would say this is being not clinically meaningful.

I think also if you compare to recent data that has been presented with other recent agents, such as in Atremis [misspelled?] and in Castle, you will also note a fairly significant drop off or at least the difference between patients in low Viral load and high Viral load with the different back bone in Epzicom.

PAPA SALIF SOW, Ph.D., M.D.: One very brief question and that is it.

BOB BRIGA: Bob Briga [misspelled?], from London. I was going to ask two questions but I will just start with the first one. You have shown us some graphs by 48 weeks and by 96 weeks which shows comparable efficacy in terms of virological survival. Now although virological survival was estimated by using the same endpoint at the ACTG5202, comparison just at fixed weeks, 48 or 96 weeks, is not the same at the primary analysis in the ACTG5202.

And in particular, if there is a higher failure rate early on but then patients catch up in the Abacavir 3TC you would not see the differences which were shown in the ACTG

study. So have you done any analysis by just looking at the hazard ratio across follow up in all these studies?

KEITH PAPPA: I do not believe we have but I guess I just would make the point again that we included data from all these studies, from the various earliest time point onward, I guess again the main point and I take Joe Erran's point certainly seriously, I am not raising that 5202 is anything but unique.

I am not indicating that it does not have solid data and very good data. But if you do look at those earlier time points, what I can say is that the failure rate is higher than what it is in these six recent clinical trials. So again that is the point that I am trying to make.

PAPA SALIF SOW, Ph.D., M.D.: We're going to move on to the next paper. Thank you very much. The next paper is entitled "Use of Nucleoside Reverse Transcriptase Inhibitors and Risk of Myocardial Infarction in HIV-Infected Patients Enrolled in the SMART Study," and it is being presented by Jens Lundgren on behalf of the SMART/INSIGHT and D:A:D Study Groups. Jens.

JENS LUNDGREN: Thank you very much. It is a privilege and an honor on behalf of the SMART/INSIGHT and D:A:D Study Groups to share this paper with you.

The background for this analysis is that we both reported in Lancid [misspelled?] in April of this year that

Abacavir was associated with excess risk of myocardial infarction.

The signal was characterized and was present for current use but not for cumulative or past use, suggesting that Abacavir may increase the chance that existing atherosclerosis converge to cardiovascular disease.

Robust, this finding was robust after adjusting for cardiovascular risk factors suggesting that channeling bias for known cardiovascular risk factors is less likely as an explanation for the findings.

The aims of the present analysis was to establish whether this finding can be reproduced in another data set, where the utilization of various nucleosides and nucleotides, abbreviated NRTIs differed from that in D:A:D and furthermore to explore both biological mechanism for the effects.

SMART was a randomized trial that compared two strategies of using and switch one treatment. For the present analysis for the clinical outcome data, we focused on all patients that would randomize to the VS Arm and the Virus suppression arm. I am going to show you biomarker levels of six markers of inflammation and correlation of study entry among patients who already, when they entered into SMART on NRTIs, that will be for 791 patients.

Now just for clarity, use of NRTIs in this presentation, we divided patients into three mutually-exclusive groups. Those on Abacavir, not receiving didanosine inside of

that ABC non DDI group. The second group was patients receiving didanosine with or without Abacavir and other nucleosides inside the DDI group. And then finally, NRTIs other than the ABC and the DDI was entitled others.

This graph shows you the entire population of patients that were on nucleosides when they entered into SMART. I could have shown you similar results for the 2,752 patients that were randomized in the VS Suppression arm that constitutes a population of patients from a clinical outcome data as well as the 791 patients that was included in the biomarker findings, the results would be the same. I have only time to show one of these tables.

You would see that at entry, the age of the patient were 44 years, 27 percent were female, suppression rate was 83 percent, remind you everybody is on treatment, CD4 cell count is 630, 4 percent had a history of cardiovascular disease, 39 percent were current smokers. We did in a subset of patients baseline ECG and among those with an ECG available at study entry, 36 percent had evidence of ischemic abnormalities, 7 percent had a history of diabetes.

Furthermore, in the same population of patients, 19 percent was using blood pressure-lowering drugs, 18 percent lipid-lowering drugs, the total to HDL cholesterol is 4.6, mind you that a normal ratio should be at 4.5 or below, 31 percent were either in the past or currently using Abacavir, of course

100 percent in Abacavir group, 28 percent in the DDI group and 7 percent in the other group had previously used Abacavir.

Thirty nine percent of the Abacavir patients were taking it with NRTIs exclusively and that percentage was much lower than it's two other arms, 21 percent were using tenofivir, 15 percent of this cohort had five or more cardiovascular risk factors at entry.

I am going to describe the four outcomes. These outcomes are all pre-specified either in the publication with the journal from 2006 or in a follow-up in publication by Endo Philips [01:09:53] in antiretroviral therapy early this year. Of note, all events are adjudicated by the endpoint review committee.

We operate with cardiovascular major events which will be clinical or silent MIs, strokes, surgery for coronary artery diseases, cardiovascular death. For the examples since myocardial infraction, clinical MIs were the primary endpoint in D:A:D, we also singled that at single endpoint note.

We did also an expanded version of the major endpoints of which in addition to those I mentioned above also included peripheral vascular disease, congestive heart failure for our treatment for coronary artery disease in un-witnessed death.

Finally we operate when a third major outcome inside the minor cardiovascular disease which is congestive heart failure, peripheral vascular disease or coronary artery disease

requiring drug treatments. This is the main analysis of the findings.

On this slide, we are comparing the hazard ratio of experience either of the four events shown on the left side of the slide in patients that was either currently receiving Abacavir or other NRTIs. You would appreciate that the number of endpoints differs, in particular we only had 19 patients with an MI.

The highest number of endpoints that we have is the expanded definition of the major cardiovascular disease endpoints. If we focus on this point in particular, the hazard ratio was 1.9 which was exactly the same as was found in DAD and you will appreciate four 4th endpoints. It is in similar directions suggesting an association between current use of Abacavir and excess risk of these outcomes.

I should mention that these analysis are presented either unadjusted or after adjustment for cardiovascular risk factors. If you focus on the adjusted values for Abacavir and then also present the data for the patients who were receiving DDI with or without Abacavir, you would appreciate the confidence interval for patients that belongs to this group for these outcomes, are much wider than for Abacavir given the smaller number of patients and also that for all four outcomes, the confidence interval only had one and for three of them, the hazard ratio was exactly one.

Of note, for the primary endpoint in DAD and in myocardial infarction, we see the same trend as we saw in DAD although the power to detect [inaudible] is of course, much more limited. I need the next slide. Thank you. Somebody is playing with my slides. I want to go forward. I need the next slide. Next slide, next slide and the next slide. Thank you.

This slide gives you the hazard ratios for using Abacavir verses using other in ITI's according to cardiovascular risk datas at study entry. At study entry we started to file the patients into those who have five or more cardiovascular risk factors or those who had less so. Also, for the subcrural [misspelled?] patient where we had baseline EGT, we started to file patients into whether they had baseline ischemic abnormalities or no.

We then compared whether the axis ridge of the expanded definition of major cardiovascular disease endpoints were seen more frequently in patients that fulfilled these criteria as opposed to those who did not. There is an apparent further access risk in those who fulfilled this endpoint although, you should note that the appropriate statistical way of testing for differences between those two is an interaction analysis and the P value was 0.1 i.e. not significant. The P value was even remotely insignificant focusing on this.

In addition, we explored based on baseline biomarker levels, whether there was any difference in biomarker levels, that at study entry among patients who already, when they came

into the study, was a nucleus side in ITI's, depending on whether that was an ABC DDI or other. So, you can compare the labels that is shown for Abacavir and DDI. We have shown the median levels in the other group below the slide.

You would appreciate that after adjustment for cardiovascular risk factors and other factors, we saw a 27-percent higher level of high sensitivity CRP and a 16-percent high level of aisle 6 in patients that were on Abacavir study entry as opposed to those in others. Such differences in biomarker levels were not observed in patients that were on DDI.

They said provide you with limitations in these analysis. These are sensely observation analysis leading to the possibility of channeling bias i.e., that patients had a priori excess underlying risk of cardiovascular disease may have been preferentially placed on Abacavir.

Of note, I have shown on previous slides, cardiovascular risk factor profile was fairly comparable between groups and furthermore, and more importantly, adjustment for known and quantifiable cardiovascular risk factors failed to affect their association.

Of course, the definitive solutions for this question is to perform a randomized control trial which would require at least 15,000 patients and last for two to three years.

Another limitation is that there is a possibility that patients on Abacavir have elevated high sensitivity CRP and I6

labels for reasons other than use of Abacavir. The way to probably solve this is to perform prospective follow up studies looking at percent changes for individual patients. Again, preferentially in the randomized control trial setting.

For some of the endpoints we have limited power and then finally in terms of overlap of patient populations between those in DAD and SMART, some of the sites do participate in both trials but when we focused on sites that do not participate in DAD, they contributed to more than 90-percent of the endpoint shown and in that group of patients, the findings that I have shown you are not entirely consistent with those that are presented here.

So, in summary, consistent with DAD current use of Abacavir, doing follow up in SMART was associated with an excess risk of cardiovascular disease and furthermore, Abacavir use in study entry is associated with increased levels of iron 6 and high sensitivity CRP.

Our proposed mechanism for [inaudible] action for how Abacavir may increase cardiovascular risk. It is that the drop courses in increased propensity for subclinical already existing atherosclerosis to cause cardiovascular disease. The data not consistent with Abacavir affecting the atherosclerotic process per se.

The increased propensity may be caused by properties of the drop in iron 6 and high sensitive CRP made the circuits of

ongoing inflammatory actions in the coronary artery wall leading to instability of existing plaques.

So, in conclusion, Abacavir is associated with excess cardiovascular risk in two observational studies. The drop does not appear to affect the underlying atherosclerotic process per se, but may cause coronary arteritis that lead to instability of plaques. This adverse affect appears to be only clinical relevant to consider among patients with elevated underlying cardiovascular risk.

I should note that a manuscript is impressed as fast track in AIDS with an aim publication date of the second of September of this year. I would want to make note and acknowledge my co-authors in particular, Jim Neaton, Jackie Neuhaus, and Birgit Grund from the statistical center at University of Minnesota where this analysis was performed as well as to the study groups as well as to NIAH that supported SMART. Thank you for your attention. [Applause]

JULIO MONTANER M.D., F.R.C.P.C., F.C.C.P.: Jens, thank you for that very eloquent presentation. Could you come in on the high number of people that were on nucleosides alone in this study and could you speculate on HLA bicarbonate connection.

JENS LUNDGREN: Sure. That is a very good question. We of course thought whether this is essentially an auto manifestation hypersensitivity reaction i.e., just another phenotype of having HLA B5701.

Of course, that phenotype of the hypersensitivity reaction will present itself within the first three months of starting the drug to begin with but the affect that we are seeing here is in patients who have been on the drug for several years. So, it is very unlikely that that phenotype that is in that subgroup of patients where this problem exists.

JULIO MONTANER M.D., F.R.C.P.C., F.C.C.P.: But, however, as you know, only a fraction of the people who have the genotype go on to have the reaction. So, the possibility still exists that you could clean this out by using HLA.

JENS LUNDGREN: Absolutely. And the way to, I think this is a very important point, and I would encourage people who have access to genotypic material to explore this question further, it may be that haplotype, it may be other HLA haplotypes that leads to a potentially ongoing maybe subclinical inflammatory reaction in some patients.

JULIO MONTANER M.D., F.R.C.P.C., F.C.C.P.: I would actually hide number of people on nucleoside alone, that is out of normal sort of practice.

JENS LUNDGREN: Well, it is just instantly reflecting use of Trizivir and we did address in our analysis whether adjustment for that factor would be explaining the excess risk and there was similar excess risk irrespective of whether Abacavir was used together with other nucleosides or as a Abac one therapy [misspelled?]

JULIO MONTANER M.D., F.R.C.P.C., F.C.C.P.: First question.

KIMBERLY SMITH: Kimberly Smith [misspelled?], a resident in Chicago. I actually wanted to follow up on Julio's question regarding the triple nucleon, have you done an analysis excluding those individuals considering that we know that protease inhibitors by themselves have an impact on immune activation.

JENS LUNDGREN: We obviously, in SMART struggling with numbers as you would appreciate. We did however, look at that as I just explained to Julio and did not find that to affect the risk. Furthermore, we also explored that in the DAD study and the data that we had in SMART and those in DAD entirely consistent.

JOEL GALANT: Joel Galant [misspelled?] from Baltimore. Now, your abstract says that when you compared Abacavir specifically with Tenofovir as opposed to other nucleosides, you had similar findings which you did not mention that in your presentation. Can you comment on that?

JENS LUNDGREN: I had a lot of data to send in 10 minutes and one of the sensitivity analysis that we did as you are referring to was that in the other NITI group, we did take patients out in a exploratory analysis that did not use Tenofovir and found essentially the same findings as was presented on the slides. Clearly, that type of analysis is limited by the fact that we are reducing our reference group

and we really have to wait for the analysis of the DAD study group data set which have many more events where we can finally nail that question.

JULIO MONTANER M.D., F.R.C.P.C., F.C.C.P.: In the interest of the data, I am going to take the last four questions but not more, quickly.

PETER INGMAR: Peter Ingmar [misspelled?], San Francisco. Any incidents of stroke and if so, why not?

JENS LUNDGREN: I did not hear that.

JULIO MONTANER M.D., F.R.C.P.C., F.C.C.P.: Any incidents of a stroke and if not, why not?

JENS LUNDGREN: There is a few strokes that is encompassed in the definition of major cardiovascular disease but stroke is traditionally seen in HIV patients as well as in general populations much more frequently in older patients about 60. So, that is the explanation why I think we do not see as many strokes currently in HIV patients.

HAL BRICK: Hal Brick [misspelled?], San Diego, nice job Jens. You mentioned there is about 10-percent overlap in the two cohorts. Did you do an analysis that excluded the overlapping patients and did you find the same results when those patients who were overlapped were excluded?

JENS LUNDGREN: So, let me just say, I did not say 10-percent overlap, I said that if we restricted our analysis to sites that for sure did not participate in DAD, 90-percent of the outcomes, 90-percent of the events were seen in sites that

did not participate in DAD and declared these other sites in the event that drive this analysis.

We can furthermore say that in those sites that participated in both studies, that is rather limited how many patients actually participated in both. If you want to quantify exactly how many patients it is among those sites, I cannot do that because the two studies operating with anonymous data and therefore, we cannot quite cross link them. Clearly that is not explaining our findings as I was trying to do.

JULIO MONTANER M.D., F.R.C.P.C., F.C.C.P.: One final question.

MARSHAL DeSOUZA: I am Dr. Marshal DeSouza from Fort Myers, Florida, U.S.A. I have large number of patients, both of Epzicom-based and Truvada-based regiments and in the Epzicom-based regiment, both in the HLAV27013 and post, my patient seems to be doing clinically, vitalogically, and metabolically well.

So, my question is why is this divergence between the clinical trial data and the clinical data, is there any explanation? I noted the aisle 6 association and HSCRB association. Is there any other explanation?

JENS LUNDGREN: First of all, I would like to remind you that DAD is not a clinical trial but that is actually a cohort of patients that reflect the usage of the drug. Furthermore, I want to just emphasize that the finding that we

are describing here in SMART as well as we have described previously in DAD.

And the problem in terms of clinical relevance of really only seeing in a very small group of your patient cohort, mainly those who have several underlying cardiovascular risk factors and at least in the DAD cohorts, rather a few patients have that conglomerate of cardiovascular risk factors.

So, I think for most patients, this is not really an issue but for the older patients, those who have multiple cardiovascular risk factors, that I where I think we will have the sufferable patients where this may become a problem.

JULIO MONTANER M.D., F.R.C.P.C., F.C.C.P.: Thank you Jens. Thank you for a very nice presentation. Thank you Papa Salif, for your help. [Applause] Thank you all. The session is closed.

[END RECORDING]