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SHARON WALMSLEY: My name is Sharon Walmsley. I am from the University of Toronto in Canada. I am pleased, with my co-moderator, Dr. Pedro Cahn from Argentina, to welcome you to this session on newer antiretroviral agents.

I think we will all agree that the management of HIV-infected patients over the past [audio gap]. And then finally we will learn something about the development of resistance and the impairment that that can cause in the absence of routine resistance testing.

So, I think we are in for a very exciting session. Our speakers will each have 10 minutes, followed by 5 minutes for questions. We will welcome you to come to the microphone, state you name and where you are from, and please try and keep your questions short so that we can make sure to involve everyone.

So, without further ado, we will start this morning's session. The first paper will be presented by Marty Markowitz. It is entitled "Sustained Antiviral Efficacy of Raltegravir as Part of Combination ART in Treatment-Naïve HIV-1 Infected Patients: 96 Week Data." Welcome, Marty [applause].

MARTIN MARKOWITZ: Thanks, Sharon. Buenos diaz, attolos [misspelled?]. Okay, good morning. It is my pleasure, on behalf of my co-investigators and Merck Laboratories to present the 96-week data on Merck's study 004, which looked at the activity of raltegravir in combination of tenofovir and 3TC

in comparison to that nuc backbone with efavirenz. As most of you now know, raltegravir is a potent strand-transfer inhibitor of HIV integrase. It is potent in the nanomolar range and has activity against a broad range of HIV isolates.

Protocol 004 had a rather unique, two-part design. The first part was a proof-of-concept, monotherapy study which was then followed by a lead-in where raltegravir at four doses, 100, 200, 400 and 600 milligrams, in combination with tenofovir and 3TC was compared with efavirenz plus tenofovir and 3TC. The hypothesis was that raltegravir in combination with the nuc backbone would be well tolerated and show similar antiretroviral activity. The endpoints are shown here. You have heard me in the past present 24- and 48-week data, and these data have been published in the *Journal of AIDS*. Today I will present 96-week data. Please note that following 48 weeks, all four dose ranges of raltegravir were combined into a 400-milligram twice-daily dose without regard to food. Therefore, I will present the data in that manner.

So, it is one single group of 160 patients. The baseline characteristics are shown here. As you can see, the patient characteristics are well balanced with about 80-percent men, approximately 70-percent of the population non-white. Baseline RNA was 4.7 or 4.8 log. Approximately one-third of the cohort had an AIDS diagnosis. Please note that despite 96 weeks of therapy, there was only approximately a 15-percent

dropout rate in this particular study, which speaks I think to the tolerability of both regimens.

This is the primary endpoint, percentage of patients with HIV RNA values less than 400 copies, a non-complete or equal failure. You can see here that at 96 weeks both groups are identical with 84-percent of the cohort being undetectable. Please note that using an observed failure approach, in the raltegravir arm 94-percent of the patients were below detection compared to the efavirenz arm at 91-percent.

Looking at the 50-copy assay, again, there were almost superimposable results at 96 weeks with 83-percent of the raltegravir patients below detection and 84-percent of the efavirenz patients below detection. Again, on an observed failure approach, it was 92-percent versus 91-percent.

Concomitant with the reduction of viral load shown in the bottom half of this slide is an approximately 200-plus CD4 cell count increase, demonstrating that with virologic control in arms, there is a concomitant improvement in immunological status.

During the second 48 weeks of this study, 2 patients did have virologic failure and both baseline and genotype analyses at failure. Please note that the 1 patient in the raltegravir arm that met criteria for virological failure based on relapse—meaning that the patient went below 400 and then was at least 1 log about 400 copies—that patient had a completely wild-type genotype. Note that the patient who relapsed on

efavirenz had the expected M184V and the resistant mutations consistent with efavirenz exposure.

The overall adverse event profiles were similar between raltegravir and efavirenz. Drug-related adverse events were 51-percent in the raltegravir arm versus 74-percent in the efavirenz arm. These include any adverse event reported by investigators. Please note that the major imbalance in adverse events were neuropsychiatric symptoms. Most occurred early on, by 48 weeks, 13-percent in the raltegravir arm versus 29-percent in the efavirenz arm at week 48. And these persisted at 16-percent in the raltegravir arm and 32-percent in the efavirenz arm at week 96. Of note and importantly, the rate of malignancies in the raltegravir arm and the efavirenz arm were identical. Grade 3 and 4 laboratory abnormalities were uncommon, and I will show you those data shortly. Raltegravir had a neutral affect on serum lipid profiles.

These are the most common drug-related adverse events as reported by investigators. As you can see, diarrhea and nausea were rather the same in both treatment arms. The difference between the arms is really dizziness, headache, and abnormal dreams and nightmares. This predominates in the efavirenz arm.

Grade 3 and 4 laboratory abnormalities were relatively rare in both arms. I will call your attention to the fact that there were 10 reports of grade 4 elevations of CPK in the raltegravir arm compared to 1 in the efavirenz arm.

The effect on serum lipids is shown in this slide. As I told you earlier, the effects on serum lipids in the raltegravir arm were essentially neutral with no significant changes over time in the positive direction after raltegravir exposure. The changes in cholesterol, LDL and HDL, are statistically significantly different in the efavirenz arm when compared to the raltegravir arm, and the P values are shown in the final column.

In summary, at 96 weeks raltegravir had sustained antiretroviral effect, similar to the 48-week data and to EFC6521, in combination with tenofovir and 3TC. Approximately 84-percent of the patients had viral loads below the level of detection. We did not detect raltegravir mutations after 48 weeks. Raltegravir was generally well tolerated at 96 weeks. Drug-related adverse events appeared less frequent for raltegravir versus efavirenz, and this was predominantly in the area of neuropsychiatric complaints. Raltegravir had a neutral effect on total cholesterol, LDL and triglycerides.

I would like to acknowledge the fact that this was a large study done internationally, my co-investigators, and of course the team at Merck Research Laboratories. Thank you for your attention [applause].

SHARON WALMSLEY: Thank you, Marty. This paper is now open for questions. I believe there are two microphones in the main—we cannot see them from here. Perhaps I will start with the first one, Marty, while people are trying to find the

microphones. There was some discussion to the more rapid virologic suppression in the raltegravir arms at the earlier cuts of this data. It would appear now that the two drugs are performing the same. Do you think that that more rapid decrease in viral load has any clinical importance?

MARTIN MARKOWITZ: Sharon, I think that is a very important question. The difference may really reflect mechanism, as opposed to inherent antiviral activity. However, I will caution you in that in most studies the early events are true measures of antiviral potency, and the longer events are really a combination of adherence, et cetera. So, we still do not know what the clinical significance of those differences is. An excellent paper appeared in *AIDS* last year by John Murray. For those interested, I would urge you to read it. Indeed, the difference in mechanism really may be responsible.

SHARON WALMSLEY: Mark?

MARK WEINBURG: Mark Weinburg [misspelled?], McGill University, Montreal. Marty, very interesting talk, but you said that the relapsed patient on raltegravir did not have mutations at 48 weeks. When will we know what it happening between 48 weeks and later time points in regard to monitoring for resistance mutations in this cohort?

MARTIN MARKOWITZ: Okay, I am sorry if I did not make myself clear. There was 1 patient who relapsed between 48 weeks and 96 weeks on the raltegravir arm that had parent samples. That patient had wild-type virus by genotype. None

of the other patients met virologic criteria, so any of the dropout, any of the failures were for other reasons.

MARK WEINBURG: Thank you for clarification.

SHARON WALMSLEY: Is there a question on this microphone?

FEMALE SPEAKER: Yes, [inaudible] from Duquesne University in Pittsburgh, Pennsylvania. Is there a plan to do pediatric studies with this drug?

MARTIN MARKOWITZ: I do not represent Merck Research Laboratories. However, I do know that as part of their research plan, there is a pediatric program in progress.

SHARON WALMSLEY: Okay, Mike, last question from you.

MIKE GILL: Mike Gill. So, not representing that research laboratory, put your clinical hat on and say why would you not drop the dose because there is no evidence there was any difference between those people who received lower doses in the first period? As we know, that is the likely period when resistance is going to develop. As a sub-part to the question, do you think that it is logical now to do a randomization of those people on raltegravir to once daily?

MARTIN MARKOWITZ: Mike, I think you have asked a very good question. Let me just speak on behalf of the Merck team, since I am privy to some of the decisions that were made. First of all, the 400-milligram dose was selected on the basis of lots and lots of PK data. Raltegravir is an interesting drug, in that there is a huge amount of variability within the

same person and from person to person. To try to ensure that the vast majority are receiving exposures that would appear to be consistent with a good virologic response, the 400-milligram dose was chosen. It was also in light of the fact that raltegravir exposures are substantially reduced by certain drugs, such as rifampin and tipranavir. Now, again, remember that the development plan for raltegravir really focused on the treatment-experienced population and this is the treatment-naïve population. It is rare in HIV that we have actually developed drugs with different dosing plans for different patient populations. However, I think that is an interesting thought and one that certainly should be thought about for raltegravir and perhaps other drugs, particularly as we try to roll some of these drugs out to less-developed areas.

I think that based on what we know about raltegravir exposures, the 200 milligrams twice a day exposure is probably similar to what one would expect with a every-day exposure at 800 milligrams daily, so that is on the menu, so to speak, for further development plans.

SHARON WALMSLEY: Great, thanks Marty. So, we will look to further studies with this compound.

We will move on to the second paper of this session, paper 103 entitled, “TMC278 (Rilpivirine), A Next Generation NNRTI, Demonstrates Long-Term Efficacy and Tolerability in Antiretroviral-NAÏVE patients, the 96-Week Data from Study

C204," which will be presented by Mario Santoscoy on behalf of his co-investigators. Mario, welcome.

MARIO SANTOSCOY: Thank you, Sharon. Good morning, everyone. On behalf of study C204 investigators, it is my pleasure to present the following 96-week efficacy, safety and tolerability data of TMC278 (rilpivirine).

TMC278 is a next-generation NNRTI with potent anti-HIV activity against wild-type and resistant virus with favorable PK. A 48-week analysis demonstrated that 3 TMC278 every-day doses provided potent, sustained efficacy in treatment-naïve patients and was well-tolerated. TMC278 is currently in phase 3 trials.

The C204 study is an ongoing, multinational, phase 2b, randomized, controlled dose-ranging study in 368 antiretroviral-naïve patients with a baseline viral load equal or higher than 5,000 copies per milliliter and no NNRTI mutations. Its primary objective was to evaluate the efficacy and safety, dose-response relationship of three blinded TMC278 doses, 25, 75 and 150-milligrams every day at 48 weeks. In open-label active control, efavirenz 600 milligrams every day was included for comparison. Randomization was stratified for world region and by investigator-selected NRTI backbone, either AZT/3TC or tenofovir/FTC.

Demographic and baseline characteristics were well balanced across treatment groups. 33-percent of subjects were females, 75-percent of patients initiated AZT/3TC while 25-

percent of patients tenofovir/FTC. While the median viral load was similar across treatment groups, there was an imbalance in the proportion of patients with very high baseline viral loads, more than 300 copies per milliliter, 11-percent for efavirenz patients and 23- to 26-percent for TMC278 patients.

With respect to efficacy, no significant differences were observed among TMC278 dose groups or in comparison with efavirenz at each time point. A [inaudible] divergence of response rates to TMC278 and EFC6521 between weeks 16 and 32 could partly be explained by an imbalance in the proportion of patients with very high baseline viral loads, as just mentioned.

This slide shows week-48 data because it was the primary endpoint of the trial. The proportion of patients with detectable viral loads was well-maintained from weeks 48 to 96. At week 96, 71- to 76-percent of patients in the TMC278 groups, compared with 71-percent of patients in the efavirenz group, had confirmed viral loads less than 50 copies per milliliter. No clear TMC278 dose-response relationship was observed. The proportion of virologic failures across treatment groups would low and not statistically significantly different among TMC278 dose groups or efavirenz at week 48 or week 96. Overall discontinuations were comparable between TMC278 dose groups and efavirenz. Mean change from baseline in CD4 cell counts through week 48 and 96 were similar among TMC278 groups and comparable to efavirenz with no statistically significant

differences. The mean change from baseline in CD4 cell count at week 96 further increased compared with week 48.

Regarding resistance data, very few patients experienced virologic failure with resistance-associated mutations. In the TMC278 arm it was 17 patients and in the efavirenz arm it was 6 patients. Thus, definitive conclusions about the resistance profile of TMC278 could not be drawn from this study. The proportion of patients in whom treatment-emergent NRTI-associated mutations developed was similar across arms. In genotypes subjects, mutations arose in about 50-percent in each treatment arm. Resistance findings will be further explored in phase 3 trials which will include a much larger sample of patients, around 600 per arm.

There was no notable increase in adverse events from week 48. The incidences of any adverse event, any serious adverse event, any grade 3 or 4 adverse event and grade 3 or 4 lab abnormalities were similar between all TMC278 groups compared to efavirenz. Investigations reported as grade 3 or 4 adverse events were the principle cause for discontinuation in the TMC278 combined group, while no efavirenz patient was discontinued due to this.

Analysis of specific safety data, where I believe clearly the real differences between TMC278 and efavirenz lie, showed the following. Firstly, the frequency of rashes of any grade was lower for TMC278 than for efavirenz. It was 9-percent versus 21-percent respectively with a statistically

significant difference. Secondly, nervous system disorders occurred in 31-percent of TMC278-treated patients versus 48-percent of efavirenz-treated patients. Again, there was a statistically significant difference, especially regarding dizziness and to a lesser degree somnolence. Thirdly, psychiatric disorders were reported at similar incidences in the three TMC278 dose groups and at a lower incidence than with efavirenz. Only the frequency of abnormal dreams was statistically significant lower for TMC278-treated patients.

There was a clear increase from baseline for total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides for the efavirenz group. This difference with the TMC278 combined group was statistically significant. There was no increase in total cholesterol, LDL or triglycerides for any of the TMC278 dose groups. There was an increase in HDL cholesterol for all TMC278 dose groups which was not as great as in the efavirenz group.

Additional endocrine investigations were undertaken because of preclinical study data. However, no clinically relevant changes in adrenal and thyroid parameters were observed. As for ECGs, these were done as part of routine safety monitoring. Increases in QTc interval were seen with all TMC278 doses and efavirenz up to 48 weeks, which then stabilized up to week 96. Increases were primarily seen with the AZT/3TC backbone. Mean increase was lowest with TMC278 25 milligrams.

In conclusion, once daily oral TMC278 at all doses demonstrated a high response rate and sustained virologic response over 96 weeks. TMC278 was generally safe and well tolerated. The instances of rash, nervous system and psychiatric-related adverse events and increase in lipids were significantly lower with TMC278 than with efavirenz. There were trends suggesting a favorable profile of TMC278 25 milligrams compared with the higher dose groups. Both efficacy and safety of TMC278 were well maintained between 48 and 96 weeks. TMC278 is being further evaluated in phase 3 trials at a dose of 25 milligrams every day.

And finally, I would like to acknowledge the authors. I would like to thank all the patients who participated in the study, the study center staff, DSMB members, [inaudible] personnel and the following principle investigators. Thank you [applause].

SHARON WALMSLEY: Thank you, Mario. This paper is open for questions. First, I would just like clarification, Mario, on the QT prolongation. Did you imply that there were no more cases of QT prolongation after week 48, or was it the length of the QT that was not longer after 48 weeks?

MARIO SANTOSCOY: What I meant was to say that the prolongation indeed stabilized between 48 and 96 weeks. I did not show the graph which clearly shows a steeper line between baseline and 48 weeks. And then there was a much less steep line until 96 weeks for all groups. That is what I meant.

SHARON WALMSLEY: Joe?

JOE ERAN: Yes, hi, Joe Eran [misspelled?] from Chapel Hill. Could you please tell us what the rilpivirine resistance mutations were?

MARIO SANTOSCOY: Well, as I said, no definition conclusions could be drawn from the small number of patients with viral failures in this study. There were nine patients with resistance-associated mutations, which is very small. I do not believe we can say with any certainty which and how many mutations are sufficient to confer resistance to TMC278.

JOE ERAN: I think it is reasonable to just tell us what they are, do you not think?

MARIO SANTOSCOY: Well, yes. For the majority of these nine patients, there were 184V mutations found. As for NNRTI mutations, there were also some of these patients found with 138k mutation.

JOE ERAN: Thanks.

SHARON WALMSLEY: Mike?

MIKE GILL: I see that they are continuing to do their do not tell us the resistance data until later scenario, which I would argue is a bad idea. Either I was asleep, which probably could have been true, or I missed the fact that since there was no difference in the total adverse events between the four arms, if you had a significant difference in some of the adverse events, what were the trends to worse adverse events for the TMC278 arms? So, even though you acknowledge this is a

small study and it is, what were the things in the TMC278 arms that were more frequent within adverse events? Was it hematologic changes or others? It must account for the balance.

MARIO SANTOSCOY: Yes, I would say that the patients with the 150-milligram TMC278 dose were found with a higher incidence of adverse events in general. Likewise, I would say the same for the 75 milligrams. The 75-milligram dosing was used since week 48 until now, recently when we—excuse me from week—until now, week 144, it is being used—it has been changed to 25-milligram dosing. I do not know if I answered your question.

MIKE GILL: I think it is always good to be more honest about the results in earlier studies, because then it allows us to understand what is going to happen in later studies.

MARIO SANTOSCOY: Thank you.

SHARON WALMSLEY: Okay, last question at this microphone.

MALE SPEAKER: Hi. It is a bit more of a comment. I am encouraged to see this drug go through. I am really interested in drugs that can take the place of efavirenz. I just want to say that in collecting the data in the adverse events, we need more accurate reporting of what those adverse events are. Of the people who take efavirenz, 50-percent have a really difficult time and that is not dizziness. It is feeling suicidal. It is I cannot finish my thoughts. I cannot

look after myself. I cannot work. There is a whole bunch of stuff that goes in there and I just see in this conference people obsessed by Sustiva or efavirenz, so much so that I had to walk out the other day because everyone wanted a tripla. I do not want convenient HIV. I want effective drugs that do not have side effects that make me go crazy. So, when we need to get these drugs paid for, those are the arguments we need to make and we need that captured in the data. If you are not doing that, you make our job very hard.

SHARON WALMSLEY: Okay, I think we would all agree that we are happy to have new agents. I think we all look forward to seeing more details on the resistance profiles and what the main NNRTI mutations are with this compound, as well as a clarification of the adverse event profile.

So, I will now turn the chair over to Pedro, who is from Argentina, Buenos Aires and is our outgoing IAS President, to chair to second half of this symposium.

PEDRO CAHN, M.D., PH.D.: Thank you, Sharon. Our next paper will be "A Prospective, Randomized, Open-Label Trial of Efavirenz versus Lopinavir/Ritonavir Based HAART Among Antiretroviral Therapy-Naïve, HIV-Infected Individuals Presenting for Care with CD4 Cell Counts <200/mm^3 in Mexico." It was done by Juan Sierra Madero and coworkers here in Mexico.

JUAN SIERRA MADERO: Thank you. I would like to thank the organizers for allowing me to present this data today on behalf of my colleagues and co-authors.

This is a 48-week analysis of an open-label, randomized trial conducted in multiple sites in Mexico to evaluate the virological efficacy of two regimens in HIV-infected subjects who were naïve to antiretrovirals and who presented to care with very low CD4 counts. In developing countries, including Mexico and in many areas of the developed world, the most common form of presentation to care of HIV-infected individuals is with advanced disease. This is defined as those patients who present with an AIDS-defining event or CD4 counts less than 200.

In fact, in a recent study presented at this conference yesterday, 74-percent of patients from different Latin American countries had a CD4 count below 200 when beginning therapy. In that study, the number for only centers evaluated in Mexico was close to 80-percent. This is important because very low CD4 counts at baseline have been consistently associated with poor virological and clinical outcomes to HAART and different studies. And even though many antiretroviral studies in naïve subjects have included sub-analyses for efficacy in patients with very low CD4 counts, there are few studies that directly compare regimens in this difficult-to-treat population. Treatment guidelines are based on studies in which most of the studies do not have advanced disease.

So, according to the most recent treatment guidelines in many parts of the world, including those from the HHS in Mexico, the options to start treatment are either efavirenz or

a boosted PI in combination with two nucleosides. Until last year, the Mexican guidelines recommended a boosted PI as a third component of an initial regimen for patients with CD4 counts lower than 100. A few studies have compared an efavirenz regimen versus boosted PIs. One such study is the recently published ACTG 5142 trial, which compared lopinavir/ritonavir versus efavirenz in treatment-naïve subjects. Of note, the median CD4 values at baseline in this study were well above 100 and close to 200. Only approximately a third of patients in each groups had CD4 counts less than 100.

So, the primary objective of our study was to demonstrate non-inferiority of efavirenz versus lopinavir/ritonavir in antiretroviral-naïve individuals with CD4 counts less than 200. The primary endpoint was the proportion of subjects with less than 50 copies at week 48. Secondary endpoints were changes in CD4 lipids and safety.

The study was conducted in 11 sites in Mexico. The blue stars indicate the location of the sites outside Mexico City. Many of these sites attend to rural and marginalized populations. The states in red are those with the highest prevalence of HIV in the country. The coordinating center was located in Mexico City. The study was registered in clinical trial website and methodological support by the Business Center for Excellence for AIDS in Vancouver.

The study was open-label and randomized and included treatment-naïve, HIV-infected subjects whose CD4 counts at baseline were less than 200. There were 264 patients screened and 189 randomized 1:1 to receive efavirenz or lopinavir/ritonavir in combination with a fixed-dose combination of AZT and 3TC. There were 75 screening failures. Among the reasons for these failures were patients having CD4 values higher than the inclusion criteria, deaths during the screening period, TB, and withdrawal of consent.

For the randomization process the patients were stratified according to CD4 values below or above 100. Patients who develop intolerance or anemia with AZT were allowed to substitute or abacavir and continue the study. There were 6 patients in the efavirenz group and 8 in the lopinavir groups who substituted during the study.

The laboratory evaluations were done at baseline then at weeks 8, 24, 32 and 48. Virological failure was defined as the confirmed presence of HIV RNA above 50 copies after six months in the study or at eight weeks failure to decline more than 1 log.

The primary endpoint was the proportion of patients with HIV RNA less than 50 copies at 48 weeks using the time to lost virologic response algorithm. The non-inferiority hypothesis was confirmed in the lower limit of 95-percent confidence interval if the difference between groups in virologic response is higher than -12 [misspelled?].

So, the baseline characteristics of the patients are shown in this table. The proportion of women participating in the study is similar to the proportion of women with HIV in Mexico. As shown by the median value of CD4—which is 64 and 5—and by the proportion of patients with CD4 counts that had lower than 15—which was almost 50-percent—this is clearly a very advanced group of patients. More than 80-percent of the patients had a viral load higher than 75,000 copies.

This table shows the patient disposition at week 48. The reasons for discontinuation from the study are shown here. Virological failure was more common in patients receiving lopinavir. Discontinuation for adverse events was more common in the lopinavir also, but not statistically significant. And among the adverse events leading to discontinuation, there were 7 deaths and 3 patients who developed tuberculosis after treatment initiation. There were 16 and 12-percent of patients who were considered lost to follow up or who abandoned the study.

So, using the 50-copy limit of detection assay by intent-to-treat analysis, shown in continued lines here, 70-percent and 53-percent of patients were undetectable in the efavirenz and the lapatinib/ritonavir groups respectively. The difference between the groups is 17-percent and meets the criteria for non-inferiority and also for superior efficacy. The difference was also significant in the as-treated analysis, shown in the other lines.

A post-hoc sub-analysis of those patients who started treatment with less than 50 cells showed a significantly higher proportion of patients reaching 48 weeks with less than 50 copies in the efavirenz group than in the lopinavir group.

Using the 400-copy assay by intent-to-treat analysis, the proportion of patients who had undetectable viral load was 73-percent and 65-percent in efavirenz and lopinavir groups respectively, and this difference is not statistically significant. In the as-treated analysis, the proportion was 88 and 75-percent and this difference was significant.

CD4 values increased throughout the study in both groups. At 48 weeks the increase in CD4 counts was similar with an average of 150 cells.

Genotypes were available on a portion of those patients who failed. All three genotypes in patients experiencing failure on the efavirenz group had mutations, whereas only one in the five patients in the lopinavir group had a [inaudible] mutation.

This slide shows the change in lipids at week 48 from baseline. The changes in total cholesterol, high-density cholesterol and low-density cholesterol were no different, but the change in triglycerides was significantly higher in the lopinavir/ritonavir group.

During the trial, serious adverse events occurred in similar proportions in both groups. Most of these were opportunistic infections leading to hospitalization and death.

Among them, 2 to 4 adverse events experienced—suspected CNS disorders were more common in the efavirenz groups, and lipid disorders were more common in the lopinavir group.

So, in summary, the results of this trial in naïve subjects with advanced HIV disease show a significantly higher proportion of subjects achieving a goal of less than 50 copies at 48 weeks in the efavirenz arm by intent-to-treat analysis. The difference in highly significantly in favor of efavirenz and is given both by the higher rate of virological failure in the lopinavir group as well as a higher rate of discontinuation. And it is important to note that the difference was not significant in the 400-copy assay, which implies that most failures in the lopinavir group are occurring with viral loads in the range between 50 and 400 copies. The other finding of the study confirms findings from other trials showing a higher impact on triglycerides with lopinavir/ritonavir regimens.

We accept that this study has important limitations. Since the study was conducted only in Mexico, results may not be generalized. However, similar results have been observed in other trials. While there was a relatively significant rate of abandonment observed, it was similar among groups and may be explained by many factors, such as the high proportion of subjects coming from marginalized areas. Another factor may be the use of AZT as the nucleoside backbone, which may be associated with higher toxicity, especially in patients with

advanced disease. While this is an important limitation in a study such as this, this is also a true reflection of real life in many regions in the country.

Genotypic resistance was not done at baseline. However, this is not a standard practice currently in Mexico because of costs and the low prevalence shown so far of primary resistance. The other factor is that we used lopinavir capsules, which may have contributed to a higher pill burden.

So, until we improve our capacity to detect HIV infections in earlier stages in those regions of the world in which HIV disease is presenting at such late stages, we will continue to fact the challenges that involve treating this group of patients. I think that new studies should also focus on this population. Thank you [applause].

PEDRO CAHN, M.D., PH.D.: Thank you, Juan for this excellent presentation. It was remarkably similar to the results of the 5142 study. I think we have Joel Gallant at the first microphone.

JOEL GALLANT: Joe Gallant from Baltimore—I may have missed it, but it looked like you were using a higher-than-standard dose of lopinavir/ritonavir.

JUAN SIERRA MADERO: I did not hear the question. We use the dose 3 capsules two times a day of lopinavir/ritonavir. I am sorry. I did not put the acknowledgments and the funding from the study. The study was funded by [inaudible] Mexico in part and by the Department of Infectious Disease, the Hospital

of Nutrition, and [Spanish Spoken], in case people want to know.

PEDRO CAHN, M.D., PH.D.: Mike?

MIKE GILL: So, I am feeling very sparky this morning. I promise I will not ask any more questions. That was a very nice study, but I think it really is the hare and the tortoise. Do you want to have early virology help, or do you want to have lots of resistance when you fail? My question is more related to the presentation of adverse events and the relationship between the fact that you see a higher CD4. It was not statistically significant with the small sample size, and it was the same in ACTG 5142. You get a better CD4 response with lopinavir/ritonavir. Is that related to IRIS or to IRIS-like syndrome, or even to the therapy of emergent macrobacterial disease? So, did you have an imbalance between the arms a proportion of patients that developed IRIS, and how do you think that relates to the CD4 rise?

JUAN SIERRA MADERO: That is a very interesting question. Unfortunately, we did not plan the study to look for IRIS and now we wish we had. As you know, defining IRIS is so difficult and you have to do it prospectively. Retrospectively, it would be very hard to go back and check for that. Thank you.

PEDRO CAHN, M.D., PH.D.: Richard?

RICHARD: I am from San Diego. I was going to ask a question quibbling about the non-inferiority sample size

calculation, since you had a much lower sample size than a superiority study that we did in ACTG 5142, but I actually will not ask that question. I just have a comment on the CD4 increase. I could not tell because numbers were small, but we saw about a 50-cell increase in the lopinavir-containing arms compared to the efavirenz arm across all the CD4 strata. Although statistically significant, we did not see any difference when we looked for thresholds, i.e. did you get more patients above a critical threshold like 200? Did you do such an analysis to see if there were more patients that got above 200 cells between your two arms?

JUAN SIERRA MADERO: We did not look at it that way, but we can do it. With respect to the sample size, I also agree that the study actually was powered with a higher number of patients originally to meet non-inferiority criteria. However, we had to stop recruiting for this study because of funding problems, and we proceeded with a study such as this and we will found differences.

PEDRO CAHN, M.D., PH.D.: Okay, thank you, Juan. We are moving to our next presentation. I am sorry. We have time for one more question, yes.

FEMALE SPEAKER: Yes, do you think using capsules for the lopinavir introduced a bias into the study compared to efavirenz? Efavirenz did not have capsules and there was a pill burden obviously for the group that used the lopinavir.

JUAN SIERRA MADERO: The fact that we used capsules may obviously increase the pill burden for patients and probably have more problems with adherence. I do not think that the gastrointestinal problems would be different from the data that I have seen with the tablet formulation, so I do not think that would be a problem.

PEDRO CAHN, M.D., PH.D.: Thank you, Juan. We are moving to our next paper, which will be "Resistance Profile of Patients Failing First-Line ART in Malawi When Using clinical and Immunologic Monitoring," by Dr. Hosseinipour.

MINA HOSSEINIPOUR, M.D.: Thank you. I would like to first thank the organizers for letting me stand up in this very big room and give the findings of our study, and I am glad to present this on behalf of my fellow investigators.

The Malawi Antiretroviral Program has now started over 150,000 patients on D4T, 3TC and nevirapine. As we know, over time a substantial minority will have virological failure and eventually clinically failure. In failing patients, resistance will be present. Today there is few data from African settings with resistance patterns, particularly where clinical and immunologic monitoring is done.

As we know looking at failure, virologic failure occurs initially and then progression to an immunological and clinical failure will proceed. We also know from developed world settings that resistance accumulates to a degree over time, although virologic monitoring is primarily used in these

settings. Given the combination that we are using, we can expect that the 184V will be one of the first mutations that will develop, followed by NNRTI mutations and then thymidine analogue mutations. We do not actually know what will be happening as we progress further along the continuum. The Malawi ART diagnosis is going to be made in the latest stages because they use immunologic and clinical diagnoses for failure.

Our second-line regimen in Malawi is tenofovir, zidovudine, 3TC and lopinavir/ritonavir. And the success of this regimen depends on the number of active drugs at the time of starting the regimen. This would depend on how much resistance had accumulated and the potency of the individual drugs. One thing fortunate is that lopinavir/ritonavir should not have any resistance mutations in this setting.

This was a prospective study of patients who were starting second-line antiretroviral in Malawi. One of our objectives was to study the resistance patterns of patients failing first-line treatment. These were HIV-positive patients who were more than 13 years old and they had been started on D4T, 3TC, nevirapine, although they may have changed to alternative first line, which includes zidovudine substitution in the event of D4T toxicity and efavirenz for nevirapine. It was a two-center study at the Lighthouse Clinic and Community Central Hospital and the Antiretroviral Clinic at Queen

Elizabeth Central Hospital, which is in Blantyre. Our enrollment was from December 2005 to June 2007.

The clinical ART failure definition for Malawi is a new WHO stage 4 condition or a progressive stage 4 condition. The immunologic ART definition is a greater than 50-percent decline from the peak or below pretreatment values. For our study, we confirmed antiretroviral failure with an RNA greater than 400 and we performed resistance testing if the viral load was greater than 1,000 copies. We used the TruGen for genotype analysis and monogram for the phenotype. Our mutations were defined per IAS USA guidelines.

We had 96 patients who were identified as antiretroviral failure with a viral load of greater than 1,000 copies. Of them, 16 had met clinical failure definitions, 87 had immunologic, and a number of them had both. Of our subject, 66 were on D4T, 3TC and nevirapine at the time of failure diagnosis and 30 were on zidovudine and 3TC as they had developed D4T toxicity. Two of our samples did not amplify, so we had 94 samples available for analysis.

The characteristics of our patients at the time of failure were as follows. The median age was 38. CD4 was very low at 68. The viral load was 52,000. And the duration of antiretroviral treatment was 37 months. And we had 50-percent female subjects. As you might expect, we had a high rate of the 184 mutations with 81-percent of the patients having this mutation, 93-percent of the patients had NNRTI mutations with a

median of 2 and 181C, 190A and 103N were the most common. We had wild-type virus in 5-percent of the samples. We had no patients who had only 184V and only 2-percent of patients had only NNRTI mutations. And 16-percent had only 184V and NNRTI mutations. So, for the other 77-percent of the patients that we saw, they had very complex mutations, and this is the group that we phenotyped as well. But 56-percent of the patients had TAM, 23-percent of the patients had tenofovir mutations, the K65R and K70E with the K65R occurring more frequently. And 7-percent had both tenofovir and TAMs and 19-percent of the patients had a Q151M complex.

If you put this together, the people who had Q151M and tenofovir were 16-perecent. We also had a patient with a 69 insertion. So, based on these resistance patterns, you would expect that 17-percent of the patients would have pan-nucleoside resistance. Among the patients with TAM, 28-percent had 1, 28-percent had 2, and 44-percent of the patients had 3 or more TAMs with a 215, 67N and 70R being the most common.

We performed a multi-varied analysis adjusting for sex, viral load, CD4 count, the use of AZT and the type of failure to evaluate the emergence of K65R or 70E. And we found that having a very low CD4 count, less than 100, at the time of evaluation had an increased risk of nearly 6-fold for developing this mutation. The presence of using AZT at the time of failure was associated with a marked decreased risk in the presence of these mutations.

We did a similar analysis looking at the pan-NNRTI resistance and again found that having a low CD4 count at the time of failure diagnosis was associated with a nearly 10-fold increased risk of having these resistance mutations. Again, AZT was protective.

We also looked at the emergence of greater than 3 TAMs as an outcome. Again, having a low CD4 count was associated with an increased risk, but in this case the use of AZT was associated with a higher risk of having 3 TAMs.

When we looked at the ART backbones that might be chosen and whether there would be two fully active drugs, in our first column we have the samples that we actually did a phenotype on and then this is our total sample, with the assumption that those that did not have the complex mutations would probably be fully sensitive. But among two fully active drugs, emtricitabine/tenofovir would only have 2-percent with fully active drugs, Abacavir/didanosine was 1-percent, and zidovudine/lamivudine/tenofovir was 21-percent. Looking at no fully active drugs, emtricitabine/tenofovir would be 29-percent, abacavir/didanosine would be 50-percent, and zidovudine/lamivudine/tenofovir would be 22-percent. And we used the lower limits of the monogram assay to be more conservative.

The limitations of our study were that we did not include all virologically failing clients because we do not do viral load monitoring in our program. And we are also unable

to know the exact duration of virologic failure for these patients because we do not do viral load monitoring. Using the lower CD4 count, we were estimating this might be a good surrogate for duration of failure. The circulating genotype at the time of failure might not represent archived resistance, such that those patients who had changed to AZT, had they been failing when on D4T, we may have had more K65R or 70E mutations. And the phenotype cut points for monogram actually applied to clade B virus and might not be as useful for clade C, so we used the lower limit.

Our conclusion is that extensive resistance is present at the time of ART failure when you use immunologic and clinical monitoring, 17-percent would be predicted to have no active NRTIs by genotype. AZT appears protective for the emergence of tenofovir and pan-nucleoside resistance mutations, but increases the risk of having greater that three TAMs at the time of failure diagnosis. And 22- to 50-percent would have no fully active drug by phenotype, depending on which NRTI backbone you chose. Zidovudine/lamivudine/tenofovir, which is the choice of Malawi, actually was the most likely to have two active drugs and the least likely of having no active drugs. In settings where clinical and immunologic monitoring is used, predominantly with stavudine-based first-line treatment, it seems that zidovudine/lamivudine/tenofovir is the most likely combination to have active drugs. And abacavir/didanosine

probably should not be recommended as an empiric backbone to change to in these settings.

I would like to acknowledge all of my colleagues, and also especially the Malawi National AIDS Commission, who funded the majority of this study and Monogram Sciences, who supported the phenotypes [applause].

PEDRO CAHN, M.D., PH.D.: Thank you very much for this really interesting study. We are lacking studies about resistance in the developing world, so I think that is a very important contribution to this conference. The floor is open for questions or discussion. Microphone two, over there?

MALE SPEAKER: My name is [inaudible] from Northwestern. I have a couple of questions. Can you comment on the recent *Lancet* paper, published by Philips and others, in which they basically did mathematical modeling and concluded that virologic monitoring was not really that important [inaudible] the mutant status? And secondly, I would like to suggest that your conclusion that AZT is protective is probably right, but you have look at it in the context of duration on stavudine because all the patients started on stavudine and then they were switched to zidovudine. People on zidovudine were those who were on stavudine for a shorter duration of time, so you have to correct for the duration of time or duration of treatment on stavudine before we can make that conclusion that zidovudine was protective.

PEDRO CAHN, M.D., PH.D.: Thank you for your comment. David?

DAVID COOPER: David Cooper from Sydney. I agree that these are very compelling data and they are starting to emerge from other regions, like Asia as well, so I think it is a global phenomenon. What I would like to ask you are the implications for guidelines, because if the guidelines continue to recycle nucleosides, which have a very high chance of not working, that is just going to increase toxicity and not provide a very happy outcome for second line. So, I would be interested in how you feel about that.

MINA HOSSEINIPOUR, M.D.: Well, I do not know if I was supposed to comment on the first speaker about the paper, so I will mention that. Actually, their estimates on the modeling did closely predict the percentage of NNRTI and 184 mutations, but I think it slightly underestimates the K65R and the tenofovir mutations, so there might be some problems with the model, and I guess I will chat with somebody at some point about that.

As far as implications, I think that probably we are lucky that we are using lapatinib/ritonavir as the protease inhibitor because it has such great potency. I think as we look at the efficacy outcomes of this study, since we have been following the patients since they started second line, we can stratify according to their level of resistance at the time. And if we see that there is particularly good response in the

patients, than studies potentially looking at lapatinib/ritonavir monotherapy or alternatively looking at a new class of drugs in combination with lapatinib/ritonavir might be better for second line to actually empirically add another class of drugs, since this particular strategy does seem to develop a lot of resistance.

Viral load monitoring has to eventually come into the forefront of how we are going to manage these people. I do not mean necessarily the standard HIV RNA that we do, but really coming up with a feasible method of monitoring viral load needs to be a part of treatment in developing countries. I think that most of the posters that I have looked at show that we are all coming to the same conclusion that you need viral load monitoring to some degree in order to really be able to prevent this emergence of resistance and preserve NRTI agents for future use.

PEDRO CAHN, M.D., PH.D.: Mark?

MARK WEINBERG: Mark Weinberg, McGill University, Montreal. I enjoyed your study very much and commend you for the thoroughness of the analysis. One question is that you have obviously shown us that K65R seems to be appearing with somewhat higher frequency in a Malawi population than might be the case elsewhere, but you did not tell us if it is appearing in the context of particular nucleosides, so can you add any information in terms of specific drugs potentially being able to select out 65R in the context of the analysis?

MINA HOSSEINIPOUR, M.D.: In our study, actually all of the K65Rs, except for two, were in patients that had been on stavudine. The two patients who had it were only one month and four months on AZT treatment at the time that we evaluated them. So it seems that it is very clearly stavudine that is selecting for this K65R.

MARK WEINBERG: So, I would simply point out that that is consistent with data that we reported earlier with colleagues from Botswana. I think we should perhaps stop referring to K65R as a tenofovir-related mutation and understand that it is really a mutation that is selected by multiple nucleosides, especially perhaps in the context of subtype C viruses.

PEDRO CAHN, M.D., PH.D.: Okay, we have no more time for questions, so we will move on to our last paper. And this paper will be presented by Susan Cox and co-workers. It is called “Safety Profile of Apricitabine, a Novel NRTI, during 24-Week Dosing in Experience HIV-1 Infected Patients.”

SUSAN COX: Thank you. I would like to start by thanking the organizers for this opportunity to present the safety data on apricitabine. I feel that safety and tolerability is an important point for us to consider. We do need new active agents, but we also need agents that are safe and well tolerated because poorly tolerated agents are difficult to adhere to and also have great impact on the quality of life of the patients. So, this presentation will

focus on the safety profile of apricitabine, which is a novel NRTI, during a 24-week dosing period in experienced HIV-infected patients.

Some background on apricitabine—it is a deoxycytidine analogue and it is a new NRTI which has a very promising profile in patients who are resistant to other NRTIs. I think the previous speaker has given us some very fine illustrations of the need for new NRTIs which have activity against the common NRTI resistance mutations that occur in failing patients.

Previous data on the efficacy of apricitabine have been presented, first at the IAS meeting last year in Sydney where data on the 21-day period of monotherapy were presented, showing that ATC provided approximately an 0.8-log drug as a monotherapy in experienced patients who were failing therapy. This was followed up this year by a presentation at Croix where a poster was presented on the 24-week data, showing that apricitabine was able to result in 70-percent of patients having less than 50 copies after 24 weeks and a rise in CD4 cells of over 250 cells. So, those antiviral data are all available. I will not focus too much in this talk on the antiviral data, although I believe they are extremely promising. This talk will focus more on the safety and tolerability data.

The preclinical data that we have on apricitabine suggests that it should have a very good profile. It has a

very low propensity for mitochondrial, hepatic, or bone marrow toxicity, all of which can be concerns with this NRTI class. We also have good activity in the presence of the 184 mutation—which, as you heard earlier, is an extremely common mutation—on its own or when accompanied by other TAMs or other NAMs in the reverse transcriptase.

The study design of the 201 study—patients were failing their current regimen with a presence of 184V. They may also have had other mutations, which I will go on to tell you about in the next [inaudible] and CD4 cells of greater than 50. They were randomized either to receive 600 or 800 milligrams of ATC or to continue on 3TC in a blinded fashion. So, initially there was a 21-day period of this functional monotherapy, during which we were able to establish the absolute contribution of apricitabine as the sole change in those patients. And under those conditions, it provided an approximately 0.8-log decrease at day 21. At day 21, all patients had their background therapy optimized according to their genotype at screening. They then continued on to week 24. At week 24, all patients were offered open-label ATC and then they continued on until week 48. We expect to present the week 48 efficacy data at a future conference later this year.

The data I will present to you now are the safety and tolerability data at week 24 comparing the two ATC arms and the 3TC arm. Baseline characteristics are shown here in this slide. As you can see, we had a mean age of around 40. Around

one-third of the patients were female, which is encouraging. We had a few patients with an initial viral load of over 100,000, as you can see there, but not many. And then as I mentioned, at baseline we had roughly half of the patients who, in addition to the 184V mutation, had one or two TAMs. For the rest of the patients, around half of the patients had 184V with three or more TAMs at baseline.

The initial presentation of the summary of adverse events up to week 24 is shown here. And you can see that for the ATC arms there were some patients who did not report any adverse events at all up to 24 weeks, whereas none of the patients in the 3TC arm achieved this. The overall presentation is fairly similar, as you can see. The exception is that slightly more patients reported grade 3 or 4 or severe AEs in the 3TC arm. And we also had three patients who reported serious AEs in the 3TC arm, compared to none of the patients on any of the ATC doses. We did not have any patients withdraw from the study due to AEs, although, as noted, one patient in the 600-milligram ATC arm did withdraw at week 20 owing to pregnancy.

Looking at the absolute number of adverse events occurring up to week 24, again you can see it is fairly similar between the two ATC arms and the 3TC arm. Most of the AEs were mild or moderate in nature, as you can see. There were slightly more severe AEs in the 3TC arm than in the ATC arms.

And again, we had 5 serious adverse events occurring in the 3TC arm, compared to none at all in either of the ATC doses.

The treatment-related AEs and the SAEs—we had five patients who reported adverse events that were determined by the investigator to be possibly or probably related to ATC. We had a mild diarrhea and mild dizziness in one patient on the 600-milligram dose. We had mild nausea in one patient on the 600-milligram dose, and that patient did temporarily interrupt study drug, though then restarted without further problems. We had a mild pyrosis on 800 milligrams, mild anorexia and moderate weight loss on 800 milligrams. And we had a mild gastric intolerance and moderate diarrhea in the 800-milligram group.

There were three patients reported five AEs that were possibly or probably related to 3TC. There was mild nausea and vomiting and mild increase in lipoatrophy in one patient. There was mild facial lipoatrophy in a second patient. A moderate and then a severe exacerbation of peripheral neuropathy occurred in a third patient in the 3TC arm.

As mentioned, we had three patients who reported five serious adverse events. They were all unrelated, but they all occurred in the 3TC arm. We had a left renal calculus that occurred at week 16, we had a patient with renal insufficiency, and we had a patient that experienced a dental abscess at week 10.

Looking across the most frequent AEs that were treatment emergent between day 0 and week 24, again you can see the three arms are quite similar. The pattern of adverse events is probably what you would expect in this treatment-experienced population who were also receiving other antivirals. So, we do have representation of nausea, vomiting and diarrhea. There is some raised triglycerides, raised cholesterol. There is some dyspepsia and a few headaches. Again, this is pretty much what you would expect of this population of patients and was similar across the arms.

So, finally, to conclude, apricitabine was safe and very well tolerated over 24 weeks in combination with other background antiretrovirals. The safety profile of ATC was at least as good as that of 3TC. Importantly, we see no evidence of any peripheral neuropathy, myelotoxicity, hepatic toxicity, no increase in lactate or lipids, no increase in lipase, pancreatitis, no rash, no hypersensitivity and no renal toxicity from ATC. All of these, as you know, can be complications with other drugs. So, we feel that as a second-line treatment for treatment-experienced patients—and I think you have heard in the previously talks how important it is that we have available new drugs for treatment-experienced patients—we believe ATC provides not only very good antiviral activity, but an excellent safety and tolerability profile.

So, I would just like to finish by thanking all of the investigators and the patients and the study staff and all the

folks back in Melbourne at Avexa who have worked so hard on this study. I thank you for your attention [applause].

PEDRO CAHN, M.D., PH.D.: Are there any questions? Thank you, Susan, and we thank all the speakers for this very nice session we had this morning. We will look forward to seeing you in the rest of the conference. Thank you very much [applause].

[END RECORDING]