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**4th IAS Conference on  
HIV Pathogenesis, Treatment and Prevention  
Antiretroviral Treatment Failure in Resource Limited Settings  
International AIDS Society and  
Australasian Society for HIV Medicine  
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**LERATO MOHAPI, M.B.B.C.H.:** Okay. Good morning everyone. Welcome to this session on Antiretroviral Treatment Failure in Resource Limited Settings. I am Lerato Mohapi and I am from the Prenatal HIV Research Unit which is in Johannesburg and my co-chair is Javier Lama from Lima, Peru. Our first speaker is Dr. Mina Hosseinipour. Mina is the Clinical Director of the University of North Carolina Project in Mhlanga [misspelled?] Malawi and an Assistant Director in the division of infectious diseases at the University of North Carolina in Chapel Hill, North Carolina. Mina will be speaking to us on validating clinical and immunological definitions of antiretroviral treatment failure in Malawi. Mina.

**MINA HOSSEINIPOUR, M.D.:** Thank you for that kind introduction and thank you to, the conference for allowing me to speak about our work on antiretroviral treatment and failure in Malawi.

The Malawi area free program is a great success story, in my opinion. Over 100,000 patients have been started on the first line regimen of D4T3TC [misspelled?] and Lavarapene [misspelled?] at this time, a great increase since 2001.

And, unfortunately, we can expect that antiretroviral failure will occur in large numbers of patients when this many

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are in treatment and the demand for second line treatment will be high.

Second line treatment for us at this time is AZT3TC  
Tulofavere [misspelled?] and Lopinavir or Tonavir  
[misspelled?]. It's a more complicated regimen than our one  
tablet, twice a day. It has TB drug interactions with  
Rifampicin and also requires food. It will require lab  
monitoring, which is not a component of our first line  
treatment regimen and it does have a high pill burden.

And very importantly for a country like Malawi, which  
is quite poor, is that it is expensive, so, approximately  
\$150.00 per month per patient on treatment versus \$13.00.

And the side effects, specifically the diabetes or high  
lipids we would expect with Lopinavir are rather uncommon in  
Malawi and it isn't necessarily experience in treating these  
particular side effects.

As we will hear, there are lots of different  
definitions for failure and in lieu less virologic, some level  
of HIV RNA being detectible is considered failure.  
Immunologic, you can have a decline in CD4 count and clinical,  
in new clinical events suggestive of disease progression.

And you expect that virologic precedes clinical. In a  
setting like Malawi, where primarily clinical criteria are used

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for initiation of antiretroviral therapy, it's also going to be used primarily for clinical failure.

And so our hope is that clinical failure, everybody that would be identified would indeed be failing if this continuum was followed.

Therefore, for us it is critical to determine the best definition for our setting of antiretroviral failure to avoid unnecessary switches to second line treatment and to avoid switching too late.

This could increase drug resistance, compromising our second line regimen and could also develop severe clinical events in that the person is so advanced at the time that we are identifying them, that it is too late to salvage them.

So, we have conducted a prospective study of patients who have actually met the Malawi ART Guidelines for failure. This is a two step study that is still on going, but the first objective is to validate the ART failure definitions and the second part would be the follow up. I am focusing on the validation of the definitions of the ART failure definitions.

This is a two center study. It is being conducted at Light House [misspelled?] in partnership with UNC Project. This is the primary government sponsored clinic in Lulonway [misspelled?]. It's considered a center of excellence and is

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used for referrals for all of the central region. So, if a patient has problems, they will be referred to this center.

It is the only center in the central region that has second line treatment. Likewise, the ART Clinic at Queen Elizabeth Hospital in Blantyre is the primary referral center for the southern region. These are both large clinics with four to five thousand patients each in the treatment and so they are very large. The Light House Clinic specifically offers every six months CD4 testing; the Queen Elizabeth does not as routinely offer that.

The definition of failure in Malawi for clinical ART failure is a new WHO Stage IV condition or progressive worsening or occurrence of a known WHO Stage IV condition and the immunologic definition is a greater than 30-percent decline from the peak or the low pre treatment values.

For the purposes of this study, we compared clinical and immunologic definitions to HIV RNA that were conducted in each of the settings. If the viral load was less than 400, the definition was rejected, if it was greater than 400, we confirmed antiretroviral failure.

Also, all of the patients needed to be on at least six months of treatment before we would consider that they were a failure case and they did need to be adherent to the first line regimen based on clinic attendance and reported pill counts.

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The analysis from the end of December 2005 until January 2007, we identified 152 patients who met the Malawi ART definition of failure. Of these 75-percent were immunologic and 21-percent met the clinical criteria and six met both clinical and immunologic.

Since this is a small number, for the rest of the study I will be referring to them within immunologic adding six and clinical adding six, incase that would be a question.

These patients, the mean age was 39 years, 51-percent were female. The CD4 count mean was 182 with a range from 1 to 927, and the mean duration on antiretroviral therapy at the time of evaluation was 33 months, with a range from 7 to 120.

Of these 152 failures, 90 were confirmed to be failing. Or, 59-percent had detectible HIV RNA. If they had a clinical definition, 68-percent of them were confirmed to be failing and if they were immunological failures, 58-percent were failing.

The type of Stage IV conditions that we saw for clinical failure included KS and if we look at the confirmed failure rate for KS, you can see only 31-percent of the patients who had progressive KS would be failing, [inaudible] pulmonary TB and wasting 75-percent were failing.

Those who had esophageal candidiasis seems to be quite effective in predicting failure, 100-percent of them, but

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strangely, we only had a couple of meningitis cases but neither of them were failing.

When we compare those who will confirm virologic failures verses non failures, we can see that the failures were actually younger. There was no difference according to gender.

The duration of time the patient was on antiretroviral therapy is considerably longer than those that were truly failing 40 months versus 25 and the CD4 count was lower than that statistically significant.

A multi varied analysis comparing those to what confirmed to be failing verses those that were not, we can see that being on antiretroviral therapy greater than three years had an 8.8 times risk of failing than those that had been on less than three years, having a CD4 count below 200 was also associated with an increased risk of failing and Kaposi Sarcoma was not associated with failing.

On the multi varied analysis, sex, age, active TB and wasting were not associated with failure. So, we see looking at KS, which seems to cause us some problems, we do have some of these patients on chemotherapy that could lower the CD4 count to suggest failure.

And also, we know that KS can progress, but even if we were to exclude KS from the analysis, we have clinical failure

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with still maybe 75-percent correct and the immunologic criteria would still be 66-percent correct.

We have a small sample size despite recruiting from very large clinics and that suggests our recruiting methods. And this is particularly true for the clinical definitions.

Routine viral load testing is not done at either of these settings so we can't determine the true sensitivity and specificity of these definitions because we are not looking at those who don't meet the definition of clinical or immunologic failure.

And to be honest, the routine six monthly CD4 count is really only done at the Light House Clinic and so the recruiting from Light House is slightly different from that at Queens and also another challenge is that base line CD4 counts are not available for the majority of referral cases because of the way that antiretroviral therapy is started in Malawi.

So in general we would recommend that viral load testing should probably be used to confirm ART failure prior to switching, particularly in immunologic cases and for KS patients.

And immunologic ART failure is particularly vulnerable to misclassification. And we can look at combinations of clinical criteria, the duration of antiretroviral therapy and

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the absolute CD4 count as possible better ART failure definitions.

I would like to thank the SAFEST 2 Team which is what we called this study, and its participants, the Light House staff at Queen Elizabeth, UNC Project, Malawi College of Medicine, John Hopkins Project Lab, the HIV Unit in Malawi, and also the National Aids Commission of Malawi, which generously funded this study.

**LERATO MOHAPI, M.B.B.C.H.:** Thank you Mina. We will take some questions. Microphone 2.

**JOHN MILLS:** John Mills. It is an interesting study and I am impressed with the sensitivity of the clinical definition. My understanding is that the longer patients remain on failing regimens as defined by elevated viral loads, the more likely you are to have multi drug resistant viruses which makes choice of second line therapy more difficult, so I think that the question that would be interesting to tease out from your data is, how long the patients with clinical failure were on a failing regimen.

Because if you are using clinical failure as a queue for doing viral load testing, you may miss someone who has been failing for a long period of time.

**MINA HOSSEINIPOUR, M.D.:** Indeed that is a well known risk, of waiting until clinical failure. Practically speaking,

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Malawi is very poor and its lab infrastructure is quite poor, so the only places that are doing HIV RNA testing routinely are the two research lab that I mentioned, John Hopkins and the University of North Carolina.

So the ability to scale up and to do HIV RNA testing would be quite difficult. That is why we are doing the second part of this study, which will include genotyping [misspelled?] of each of these failing patients to see the level of resistance that they have developed and also to see how well they respond to the second line treatment and whether it varies according to how much resistance they had.

Obviously it's not ideal, but we need to come up with the best solution for Malawi that is practical.

**JOHN MILLS:** It should be possible to do HIV viral load testing for about a fifth of the cost of 1 month's second line therapy.

**MINA HOSSEINIPOUR, M.D.:** No, I agree. That is my conclusion that it's probably useful for us to be confirming testing and I think that we will need to be sending in some viral load samples.

We are also doing, in Malawi, testing to look at one year of treatment in the national level. How many people are failing, so we can get a better gage of how effective we are at one year, two year, and so forth?

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**JULIAN ELLIOT:** Hi, Julian Elliot. You mentioned that at study entry, there was an assessment of adherence by clinic visit and co [misspelled?] count. Can you just give us some more detail about, what was the threshold values for those and what were the number of participants that were excluded from study entry based upon those thresholds.

**MINA HOSSEINIPOUR, M.D.:** This is a select population, yes, and it wasn't rigorous, it was an assessment, had they come for the last six months and did they have a drug interaction that we could immediately see from reviewing their charts and noting what their pill count is, so we didn't actually end up excluding anybody, but we did not start one person who was failing because they had been poorly adherent and then we gave them adherence counseling and got them back in. So it wasn't rigid.

**LERATO MOHAPI, M.B.B.C.H.:** Okay, last question.

**CHARLIE JOKES:** Thank you, Charlie Jokes [misspelled?]. I would like to thank you for your very interesting presentation and ask you one questions, why you chose 400 as what you have called your true failure definition, because as you may know, in the WHO, current failure definitions, we have tentatively suggested about a relay of 10,000, maybe more representative of failure.

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And I also would like to ask you, what you have done, if you consider virological failure as true failure, what you have done with those patients who are clinically failing or immunologically failing and who don't have evidence of a circulating virus.

**MINA HOSSEINIPOUR, M.D.:** For 400, we used that because that is the cutoff of our viral load that we were presenting for an audience that is familiar with 400. If I looked at 10,000, it actually doesn't change things, because the majority of our patients were well above 10,000. I did not give a mean, the lowest that we have is 770 copies.

For that patient, we did change them because their CD4 count was so markedly low in their assessment of adherence. We didn't have many values that were behind. It think 10,000, 1,000, 400 would the variety of viral loads that you pick up, I think that that is a definition that varies from case to case and the evidence for using 10,000 verses 1,000 verses 400 varies according to the situation.

I think a U.S. Investigator would not tolerate 10,000 for any period of time. I think that has been made several times already, so it doesn't change our analysis very much if we look at 10,000 or 1,000 because most of our were very high. Thank you.

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**CHARLIE JOKES:** And the second question, did you allow no viral loads to overcome the clinical failure definition? Did you continue patients on first line if they have no circulating virus?

**MINA HOSSEINIPOUR, M.D.:** We continued them on first line if they, the majority of people who we were evaluating, it seemed like they had some infections that were going on. We found a number of people when they were undetectable, but they did have active TB pulmonary, which isn't a Stage IV condition, but one that needed to be treated, so in many cases, we accounted for that, but we didn't switch if they were undetectable.

**LERATO MOHAPI, M.B.B.C.H.:** Thank you Mina.

**MINA HOSSEINIPOUR, M.D.:** Thank you.

**LERATO MOHAPI, M.B.B.C.H.:** Our next speaker is Dr. Apollo Basenero. Apollo is a Medical Officer of Infectious Diseases Institute at the Makerere University in Uganda. And he will be speaking to us about the inadequacy of clinical and immunological criteria in identifying virologic failure of first line in the Ugandan experience. Apollo.

**APOLLO BASENERO:** Thank you so much co-chair and the conference of [inaudible] for allowing me to present this work.

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The title of my presentation is Inadequacy of Clinical and Immunological Monitoring and Identifying Virologic Failure, the Ugandan Experience.

So as a little background, in our first four settings, WHO commands multi antiretroviral therapy by clinical criteria and where feasible [misspelled?] monitoring HIV RNA measurement is costly.

So this is the study site, the Infectious Diseases Institute at Makerere University and it's an HIV AIDS Care Center Research and Training Center of excellence.

So the Infectious Diseases Institute Clinic started providing a free HIV care, including laboratory testing, opportunistic infection for prophylaxis and ART provision in September 2004 and by June 2007, over 10,000 adult patients were resistant in the Infectious Diseases Institute clinic.

And of these, 10,000 are active. The first line of therapy treatment at the Infectious Diseases Institute is a fixed generic combination of Trimunue [misspelled?], which consists of stuvdine, lamivudine, and verapine [misspelled?], and this is provided by the MAP [misspelled?] program of Global Fund [misspelled?].

And the other first line is Combivent Fiverinse [misspelled?], which is provided by the [inaudible] Program,

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and we would like to thank those two programs for providing us with free antiretroviral therapy clinic.

The second line is Stavudine, zebuvadine [misspelled?], DDI and rapinava boosted by ritonavir [misspelled?]. So, antiretroviral therapy at the in the Infectious Diseases Clinic is by a clinical and immunological responses and CD4 count regimen is done every six months.

Viral loads are not routinely done because of the cost and its cost is fifty U.S. dollars to do a viral load. So, because of the inability to do a vital load monitoring in all of our patients, a switch meeting was set up in 2005, August. And it was set up mainly to discuss patients that are thought to be failing antiretroviral therapy.

So, the switch meeting is attended by doctors, nurses, counselors, and pharmacists, all who work in the clinic, and during the meeting a [inaudible] presentation of suspect and failing patients is done and then the [inaudible] is reached on whether to do a viral load or employ other interventions like intensive adherence counseling.

And by the Infectious Diseases Institute policy, change from first lane, second lane antiretroviral treatment, must be approved by this switch meeting.

So the objectives of our study was to evaluate the use of a [inaudible] of care providers in a large HIV Clinic to

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determine the need to switch to a second line treatment in patients expected to be failing first line.

So the methods, when [inaudible] are presented in this switch meeting, we classify them in 3 Categories. Category 1 is clearly failing, Category 2 is patients with poor adherence and Category three is what we describe as inconclusive and in a minute, I will explain to you each of these Categories.

In immunologic failure, we find it, according to the WHO and we have two definitions. One is 50-percent drop in CD4 peak while on treatment, and then other one is the dropping of CD4 below the base line [inaudible] base line CD4.

Our idealist measurement is through self report and pill count. So the 3 Categories that we established, Category 1 which is clearly failing, these are patients with proven clinical and immunologic and if a virologic is present, when they have virologic failure.

However, counseling sessions reveal that these patients have good adherence, usually more than 95-percent. So, during the switch meeting, we recommend switching to second line; however, the point of switching we do a post count viral load.

In Category 2, these are patients with poor adherence. They have clinical and immunologic failure; however, counseling sessions reveal missing antiretroviral therapy on several occasions, usually with an ideal of less than 95.

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So, in this group, [inaudible] counseling these [inaudible] every clinic visit and will repeat a CD4 after three or six months.

In Category 3, we described this as inconclusive. They have immunologic failure, but they are clinically stable with good adherence, so in this group we will request a viral load.

So, our results are 4,200 patients studied antiretroviral therapy at the Infectious Diseases Institute since September 2004 and the majority of our patients, where I studied them in fixed generic combination of Trimune, and this consisted in 73-percent of our patients. 27-percent who have studied on Combivent fiverinse, which is provided by pikfa [misspelled?].

We generally have a young population and the general age was 37.5 years. The majority of our patients are females consisting of 67-percent. And most of our patients start on antiretroviral therapy with a relatively low CD4, with a mean of 104 in a range of 1 to 516.

So, these are our results. Since August 2005 up to March 2007, a total of 100 patients have been discussed in the switch meetings. And they are grouped according to the Categories that I mentioned.

Twenty patients were in the clinical immunologic failure group with virologic adherence. Twenty six were in the

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clinical and immunologic failure group, with poor adherence. And fifty-four patients were in the inconclusive group. They had immunologic failure but are clinically stable.

So I will give the results according to each Category. Twenty patients were in the immunologic failure with good adherence, they were all switched to second line, and at the point of switching, we managed to get viral load in 15 out of the 20 patients and none of those patients had a detectible viral load of more than 400 copies by meal [misspelled?].

In Category 2, patients who had adherence, there were three to six [misspelled?], after intensive adherence counseling for three to six month, we repeated the CD4 and in turn, out of 26 patients, consisting of 38-percent, they had the same or increased CD4 after intensive adherence counseling, so we switched them to a second line and at the point of switching, we did a viral load and it was detected in all; however, 16 out of the 26 patients consisting of 62-percent, they had a CD4 increment [misspelled?] ranging from 36 to 113, so they were not switched to a second line.

The third category, which is the most interesting one, these are patients who had the immunologic failure but were clinically stable, there were 54 and when we did the viral load, 30 out of the 54 were consisting of 56-percent, they had

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a detectible viral load of more than 400 copies for mean, and a median of 93,000 in a range of 2,000 to 694,000.

However, 24 consisting of 44-percent of these patients had a detectible viral load of less than 400 copies per mean. So what can we conclude from this, virologic infection can be detected in the presence of immunologic and clinical failure by a [inaudible] of trained [inaudible] in patients with poor adherence. Interventions such as intensive adherence counseling, and recommended before switching to second line therapy or by performing varied regimens.

Immunologic failure alone predicted virologic failure in only 56-percent of patients and this could have led to unnecessary error to switching in 44-percent of these patients, if we had not done the viral load.

So, this suggests that viral load testing should be an essential part of monitoring in resource limited settings and resources should be made available to make this possible.

I would like to thank our friends, the patients at IDI, the Switch Meeting Team, the IDI staff, [inaudible] Complex. Thank you.

**LERATO MOHAPI, M.B.B.C.H.:** Thank you. Dr. Basenero will take some questions now. Okay, microphone 2.

**HERB HARDWELL:** Hi, Herb Hardwell. I wanted to ask, and this question is actually relevant to the previous speaker

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as well, do you make assessments of nutritional status in your patients.

I ask this primarily because malnutrition can often mimic clinical and potentially even immunological failure in these patients in areas where HIV is endemic. Food insecurity and malnutrition is a real problem.

**APOLLO BASENERO:** Thank you so much for that question. Yeah, indeed, malnutrition is a challenge in a resource limited setting; however, we don't usually measure nutritional status when we are monitoring these patients, but we take their weights and follow them up, but we don't measure their nutritional status, or we don't do a BMI.

**MINA HOSSEINIPOUR, M.D.:** If I could just say that we do do BMIs routinely in Malawi and we have a feeding program for people who have a BMI below 17 and that includes a peanut based nutritional supplement for those people who have malnutrition.

**LERATO MOHAPI, M.B.B.C.H.:** I will take a question from microphone 4.

**APOLLO BASENERO:** I'm sorry, we can't hear you. Microphone floor, please. Wait for a second; you are going to receive support, to microphone, please.

**FEMALE SPEAKER:** Hi, my name is Marteen [misspelled?] from AIDS Relief, thank you for your presentation. Can you

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just elaborate a little bit more on the intensive adherence counseling and what that incorporates and basically what the intensive counseling means?

**APOLLO BASENERO:** Thank you for that question. At the Infectious Diseases Clinic, we have counselors, a group of counselors who are trained to do adherence counseling. And when we have five patients who have immunologic failure or clinic failure, usually we refer them to these counselors. And what the counselors do, they go, they take them through their values, their CD4, their big CD4, and the [inaudible] CD4, and then they interpret to them what it means. And also they emphasize the importance of taking the drugs, and if one phase of the drugs, they tell them about the second line, and because we don't have another option if the second line fails, so they take them through all that, yes. Thank you.

**LERATO MOHAPI, M.B.B.C.H.:** Okay, microphone, too.

**MALE SPEAKER:** Hi, do you have any coinfection center failing patients, immunologically failing patients, particularly tuberculosis and hepatitis B; and second question is, because you have published and it's mostly females, what is the hazard rate increase in CD4 cone in normal populations, both in males and females?

**APOLLO BASENERO:** I didn't get your first question?

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**MALE SPEAKER:** Did you develop any co-infections in the persons failing immunologically, particularly tuberculosis, hepatitis B at the time of CD4 cone, when it fails.

**APOLLO BASENERO:** Okay, thank you so much. Yes, usually we rule out opportunistic infections. If a patient is failing because of opportunistic infections, we consider that not as, if we consider that clear cut failure, because the opportunistic infections, they come in after clinical failure, right? The definition of clinic failure is presence of stage three or stage four event after more than three months of ART therapy. So if they have opportunistic infections and they have been on ART for more than three months, then we consider that a clinical failure. Yes, and then on your first question, the average CD4 rate in the general clinic patients is around outside 60, in the first one, yes. The average CD4 rates.

**MALE SPEAKER:** Is there any difference in males and females?

**APOLLO BASENERO:** I haven't noticed any difference.

**LERATO MOHAPI, M.B.B.C.H.:** I'm sorry, we're out of time. Thank you very much. Our next speaker is Dr. Sokkab An. Dr. Sokkab An is a medical doctor working as a supervisor responsible for telemedicine activities in the Infectious Diseases Department at the Sihanouk Hospital Centre of Hope in Phnom Penh in Cambodia, and he will be speaking to us about

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Predictors of Biologic Failure in a Cambodian Setting: Findings From a Cross Sectional Study at Sihanouk Hospital Centre of Hope in Phnom Penh.

**SOKKAB AN, M.D.:** Good morning, committees, colleagues, ladies, and gentlemen. First of all, I would like to thank conference organizer for inviting me to present a finding about our cohort at Sihanouk Hospital Centre of Hope in Phnom Penh, Cambodia. The subject of my presentation today is Predictors of Biologic Failure in a Cambodian Setting. Okay. As many of us are aware, the monitoring of high active retroviral data remains a challenge in a cross section in my country. And a routine viral is not available due to the high cost. That's why the virological failure is usually based on WHO 2003 clinical and immunological criteria. However, its sensitivity and specificity are unknown.

Therefore, a cross sectional study was designed to find out sensitivity and specificity of WHO to their criteria, and also to look at additional parameters of virological failure. We conducted a study with 399 patients were included. The inclusion criteria were as follows: age over 18 years old, on first line HAART more than six months, and follow-up in Sihanouk Hospital Centre of Hope.

Our goal standard to validate the WHO criteria was if you can take a viral load of more than 50 copies per mL by

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using the Roche Amplicor. All we know WHO clinical and immunological failure criteria, respectively new onset, or recurrence of WHO stage three or four condition after the first six months of HAART. And decrease in CD4 pre-therapy baseline below, or decline superior to 50-percent from peak value.

Besides WHO criteria, we also looked to following possible predictors of the later CD4, the change in CD4, over the previous six months, the total numbers [inaudible]. And also additional parameters of PPE, ART experience, number of switches, adherence, time on ART, gender and age were related, as well.

For statistical analysis, we are using [inaudible] to categorize including the change in CD4, total lymphocyte count, hemoglobin, and body mass index. Using the count of where the sum of specialty and sensitivity is the greatest.

Table 1 will show you the baseline characteristics included in our study, and its general impression of our cohort. There was similar proportion of male and female, and most of the patients were in WHO steps, with very low CD4, and my authority of the patients, they would have been taking this regimen.

Table 2 shows you the patient characteristics at the time of the taking viral load. Thirty three among 399 patients

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had a viral load of about 50 copies per mL. At the time of the viral load, the time on the regimen was almost 13 months.

These are the results of our first objective to validate WHO criteria. Most criteria failure, clinical and immunological failure, failure criteria, has a low sensitivity at 18-percent. If you combine the both criteria, the sensitivity increased only 30-percent. In contrast, specificity is high in all categories, respectively 91, 98, and 89-percent for clinical and immunological and both combined criteria. Both were used, at low, were negative T value, were high in [inaudible].

Here are the results of our second objective, the predictors for virologic failure. The univariate analysis shows that the change of CD4 in the sick man predicting viral load was [inaudible] virological failure. And in the group, we took a more viral load, there was a 341 cells in the six month preceding viral load, compared to a decrease tensor in the group with the bigger viral load. The lymphocyte count, we lost almost 360, that was caused by and associated by virologic failure.

And it was studying [inaudible] between virologic failure and being a male, or having had more than one ART switch.

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We didn't see any association between virologic failure and change in hemoglobin, body mass index, median time while on antiretroviral therapy, ART experience, and PPE.

Using the results of predicting characteristics of analyzing the baseline of CD4 and total lymphocyte count, to with the high sensitivity and high specificity, we found that the best value for the CD4 cut off were stable under three in the CD4 in the previous six months. And the base cut of total lymphocyte count was a decrease of 300 cells or more for the previous six months.

The cut off were then run in a multivariate logistic regression to predict viral failure with [inaudible] viral predictor. Finally only three predictors remained study call significant. Virological failure was three times more likely in men than in the woman. Patients with a degree of stable CD4 over the previous six months had around a two and a half higher rate of failure compared to patients in increased CD4, and patients with a total lymphocyte count decrease of 300 cell or more were almost three times more likely to have virological failure than patients with total lymphocyte count that decreased less than 300 cells in the last six months before viral load.

Based on these results, we elected to change CD4 and total lymphocyte count to refine WHO criteria, as you will see

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in the next slide. Our refined WHO criteria by combining the CD4 and change in total numbers, lymphocyte count, the sensitivities increase almost 80-percent, while specificity and post predictor value decreased to, respectively to 53 and 13-percent. Negative predictor was not affected.

Our study demonstrated the WHO criteria for treatment failure has very low sensitivity in our Cambodian setting. Our refined WHO criteria had a high sensitivity, but the PPV is still low because of the low prevalence of treatment failure. In this setting, we've seen that the high event of four positive that we refine the criteria, is an [inaudible]. And this study should only be used when a failure can be confirmed with the viral load. And the high negative predictive value can be used to identify patients that might not need a viral load to make a treatment decision.

At the end of my presentation, I would like to give my thanks to my patients who came to do the study, and I would like to give my special thanks to the people that are here. They helped me a lot in doing research and this presentation. Thank you for your kind attention. [Applause]

**LERATO MOHAPI, M.B.B.C.H.:** Thank you. We are going to take some questions now. Okay, microphone two.

**MALE SPEAKER:** Thank you, Dr. Sokkab. I am wondering if you could discuss a little bit why the men are failing more

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often than the women. There is probably a behavioral and social reason for that rather than a biological one.

**SOKKAB AN, M.D.:** Thank you for your question. In fact in our data we showed that men were more likely failure than female, but I don't know either what is the factor. I think it's a good question and interesting that I should look further. Maybe it's related to the behavior of the men in Cambodia or maybe it is related to something else. Thank you.

**MALE SPEAKER:** Did you collect adherence data as part of this study?

**SOKKAB AN, M.D.:** Yes, of course. We collected data of the adherence. In fact we have like the design on the questionnaire of the default the patient that [inaudible] adherent and [inaudible]. Thank you.

**LERATO MOHAPI, M.B.B.C.H.:** Okay. Microphone one.

**MATT BOYD:** Thank you. Matt Boyd, Australia. Doctor, there's been a fair bit of debating in guidelines about the use of the total lymphocyte count as a surrogate marker of immunological failure in settings in which access to CD4 is restricted. Your data seems to suggest that the total lymphocyte count, in fact, was a pretty good marker of what the CD4 was doing. Do you think there is enough in your data to suggest that, in fact, total lymphocyte count is an acceptable surrogate where CD4 monitoring is not available?

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**SOKKAB AN, M.D.:** I think even this small sample, as you see, only 33 patients the most is 399 patients with detectable viral loads, so even the total lymphocyte count here so like the change in lymphocyte count here showed the predictor for virologic failure, but I think I would have to say you can use it in the setting that the CD4 is not available for the multi [inaudible].

**LERATO MOHAPI, M.B.B.C.H.:** Okay. Are there anymore questions? We have got time for one more. If not, I'll hand over to my co-chair Dr. Lama. [Applause]

**JAVIER R. LAMA, M.D., M.P.H.:** Okay. Thank you. Good morning. The next speaker is Dr. Jose Carlos Couto-Fernandez from the Oswaldo Cruz Foundation in Rio De Janeiro. He will present the Drug Resistance Mutation on HIV subtypes within the Brazilian Network for HIV Genotyping in Patients Failing Antiretroviral Therapy from Rio de Janeiro, Brazil.

**JOSE CARLOS COUTO-FERNANDEZ:** Thank you for the introduction. I would like to acknowledge the organizing committee for the 4<sup>th</sup> IAS for an opportunity to show our results concerning the genotyping of HIV drug resistance in patients failing antiretroviral therapy for Rio de Janeiro, Brazil. The joint sovereignties from Brazilian Minster of Health to control the dissemination of HIV infection, one of the most important is the free universal access to the antiretroviral therapy. It

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started in 1991 with the supplying of ACT in all public health systems. This program expanded and in 1996 with the introduction of HART to monitor the efficacy of the antiretroviral therapy. In 1997, a network of laboratories was established for CD4 and viral load determination all across the country. In addition to monitor HIV drug resistance, in 2002 the Brazilian Network for Genotyping of HIV Drug Resistance was established. All these measures together have been contributing in a shift in the morbidity and mortality in HIV patients in Brazil over the last years.

Here we have the fear of the epidemic of HIV/AIDS in Brazil with a total of more than 400,000 cases and almost 190,000 deaths associated to AIDS. The estimated prevalence of HIV infection is around 0.6 and the sexual transmission is the main source of infection. But molecular epidemiology of HIV genetic subtypes in Brazil has become more complex and regionally distinct over the years. Overall, the subtype B is the more prevalent around 80-percent followed by subtype F, recombinant forms between subtype F and B and subtype C. However, in the south of Brazil, the prevalence of subtype C actually the subtype more prevalent across the world has already excessive subtype B corresponding around 35-percent of the infections in this region. The genetic diversity has many

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implications in the natural of history of HIV infection including the response to antiretroviral therapy.

Due to the prevalence we see amounting in the HIV primary drug resistance about is still relatively low in Brazil. The free universal access to the drugs and the promising number of failing patients to the therapy, the Brazilian Minister of Health established the Network of Genotyping of HIV Drug Resistance called Reno Jeno [misspelled?]. The main objectives of this network is to establish a national laboratory network able to perform HIV genotype in patients for all public health systems, evaluate new antiretroviral strategies for patients failing to respond to previous antiretroviral regimens, and the supervision of the genotype referral doctors enable them to journalize resistance data, analyzed in part of genotyping tests in the clinical, immunological, and virological evolution of these patients in addition to determining the drugs resistance profile and the prevalence of different resistance associated mutations that are [inaudible]. The prevalence of these subtypes analyzing all sequenced gene sequences.

Actually the network is composed by 23 labs across the five different Brazilian regions, and at least 300 doctors trained in HIV genotype interpretation, and more than 300,000 tests have been performed over the last five years. The

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network actually has been used in the virosec [misspelled?] genotyping system from Solara [misspelled?]. In Rio de Janeiro they have concentrated around 20-percent of the Brazilian AIDS cases, more than 2,300 genotyping analyses were performed. Here we can see the distribution of the different genetic subtypes across the eight different regions in Rio de Janeiro. The subtype B is the more prevalent followed by subtype F, recombinant forms BF in addition to seven cases of subtype C, four cases of subtype D, three African CRFs 02, and one CRF 001. Unfortunately all of these viruses [inaudible] at the map carry any drug resistance mutation.

Moving to the reverse test profile to the nucleoside where reverse transcriptase inhibitors, note that the main principle mutations associated with this class of drugs has been very low over the years. The prevalence to non-nucleosides reverse transcriptase inhibitors will observe a significant increase of the mutation K103 and probably related to the common use of these classes of drugs in Brazil. Regarding the inhibitors protease resistance profile, the mutations for plenovir [misspelled?] column 33, for atazanavir to the column 50 and for the renovir the column 54 were relatively low yet. It is important to note that zimpanovir [misspelled?] and aronovir [misspelled?] are not yet resistant in Brazil before not available at the public health system and

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can we use it antiretroviral coverage therapy regimens in the future.

Moving to the conclusions. The distribution of HIV resistant mutations in this analysis was related to the regimens used by the patients forward in the public health system, all according to Brazilian Guidelines for treating in HIV patients. We observed the circulation of HIV subtype C and D, and the first description in Brazil of the presence of the CRF African CRF 02AG, and has added CRF 01EA. The maintenance and implementation of the HIV resistance and genotyping programs in Brazil is important for the management for the patients failing HART, and to monitor the epidemiology of HIV subtypes and the prevalence of drug resistance mutations. Our results clearly demonstrate that integrated public health policies can substantially contribute for the improvement in the survival and the quality of life in the HIV patients failing HART. Thank you for your attention.

**JAVIER R. LAMA, M.D., M.P.H.:** Thank you. This session is open for questions for the auditorium. Microphone number one, please.

**MATT BOYD:** Thank you. Matt Boyd, Australia again. Could you just comment on the - I assume that the most likely hypothesis for the BF recombination is that these are probably developed from people who are being co-infected from both

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subtypes and have subsequently developed a recombinant virus. Could you comment on whether that is the case? And secondly, related to that, have you actually ever discovered any patients within your screening program - either you or the program - of patients who actually carried both types circulating independently?

**JOSE CARLOS COUTO-FERNANDEZ:** Good question. For secondary combination virus we have already identified a different part of resistance mutation associated, for example subtype B carries more resistance for nucleosides, nucleosides inhibitor for example, and a portion of F have more associated mutation to protease inhibitors. On the other hand for the second question, the importance of the circulation of this recommended virus I think is very interesting in Brazil because we have at least five CRFs, BF documented, and then back on the therapy and evolution, of course, for the vaccine development is very, very important.

**JAVIER R. LAMA, M.D., M.P.H.:** The next question?  
Microphone number two, please.

**JODY NEMMET:** Yes, hi. Jody Nemmet from Australia. I just noted the prevalence of K65R was relatively low and stable over the years. Are you able to give us a sense of the amount of tenofovir usage in Brazil and whether that's changed over that period of study?

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**JOSE CARLOS COUTO-FERNANDEZ:** Probably due to the supplying the free access of the antiretroviral therapy, but the problem is not all drugs are produced by us. We have to buy other drugs and through use in all Brazil have many rural [inaudible] problems to the use of these drugs in a country too large.

**JAVIER R. LAMA, M.D., M.P.H.:** The last question from microphone two.

**JERRY FREEDLANG:** Jerry Freedlang, Yale University. Is this database linked in any way to any clinical or epidemiologic information so it might be possible to know if some of these resistant viruses are the result of treatment failure of recently transmitted for example in new infections, is there any information about that?

**JOSE CARLOS COUTO-FERNANDEZ:** Good question. Already that is a part of our study but we have all epidemiologic information, but these barriers is only we have available the mutation partners. We are starting to follow these patients to rescue, for example and to the patient who started tenofovir and forfeited, but we are processing all this information.

**JERRY FREEDLANG:** Thank you.

**JAVIER R. LAMA, M.D., M.P.H.:** Thank you, Dr. Couto-Fernandez for your presentation. [Applause] The next speaker is Dr. Ronald Cantrell. He will present the Simple

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Assessment of Adherence to Antiretroviral Therapy Predict  
Virological Failure in HIV Infected Patients in Lusaka, Zambia.  
Dr. Cantrell is an epidemiologist at the Center of Infectious  
Disease Research in Zambia.

**RONALD CANTRELL, M.P.H.:** Thank you. I'd like to thank  
the organizers of the conference for the opportunity to present  
this research. Today I'll be discussing simple assessments of  
adherence to antiretroviral therapy and how they predict  
virologic failure in HIV positive patients in Lusaka.

As we all know, high levels of adherence to  
antiretroviral therapy are necessary for reliable virus  
suppression. In resource limited settings, routine viral load  
testing is not widely available and there are limited options  
for second line therapy. As such, the evaluation for adherence  
is critical, particularly in the public health setting where  
preservation of the first line regimens is important to  
programmatic success.

Several studies have looked at adherence in sub-Saharan  
Africa in the past five years. This meta-analysis was  
published last year and identified nine peer reviewed articles  
from seven African countries in which adherence was the primary  
or secondary outcome of interest. As you can see, there is no  
standardized measure of adherence. Eight of the nine studies  
relied on patient self report. But there are several different

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variations on what is reported, such as number of doses taken in the past three days, in the past seven days, or in between clinic visits or in the past month. And also, the threshold for defining adherence ranges from 80-percent to 100-percent.

While adherence is important in and of itself, the more important questions are does adherence correlate with good outcomes. Here we have a couple of studies where simple measures in a private care setting and more complex measures in the US both show correlation with virologic suppression. Nachega [misspelled?] used primary claims in a private sector managed care program to define adherence, and reported the dose response relationship. Patterson also measured adherence, but they used a more complex measure, using microelectronic monitoring system among 99 patients in two US hospitals. While they did show a dose response relationship, I think the small scale of the study demonstrates the difficulty that this type of measure might have in resource limited settings.

The hypothesis of this analysis is that patients with poor adherence, as estimated by simple routinely collected pharmacy prescription refill data and by patient self report, will have detectable plasma viremia.

Zambia's population of roughly 11 and a half million people is among the world's poorest and most severely affected by AIDS. In the capital city of Lusaka, 22-percent are

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estimated to be infected with the virus. ART services began in primary health care centers in the Lusaka district in May of 2004 with funding from the President's Emergency Plan for AIDS Relief, and has expanded rapidly over the past three years. Our organization has supported the Zambian ministry of health in enrolling more than 80,000 ART naïve patients into HIV care.

Because care is primarily provided by the non-physician clinician, care in the Lusaka ART program uses an algorithmic approach. The efficacy of ART is monitored with clinical exam and CD4 count. While the capacity to measure viral load began in December of 2006, viral load testing is not routinely performed. Virologic failure is assumed when patients meet the criteria for both clinical and immunologic failure. However, when these results differ, viral load testing is performed. So, if you look at the algorithm here, this is the treatment failure algorithm used by the Zambian Ministry of Health.

Patients who present with either clinical or immunologic failure are tested again in four weeks. And if they meet both criteria, then they're assumed to be in virologic failure over here. However, if they only meet one of these criteria, a viral load test is performed. This right here is our study population that we're going to be looking at today.

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So, patients included in this analysis had to be on ART for at least 100 days and have a viral load according to the district treatment failure algorithm. The outcome of interest is detectable viremia defined as greater than 400 copies per milliliter. We collected information on other exposures, such as age, BMI, whether or not the patient had adherence support, which is a buddy who knows their status and helps them with their medication. We also have lab CD4 count, hemoglobin and clinical WHO stage information.

We measured adherence two different ways. First, we looked at pharmacy refill data, and then again with patient self report. In the Lusaka ART program, all patients are tracked via an electronic medical record system, or SmartCare system. When patients report to the pharmacy to receive their medication, the dispensation is recorded, along with a date they are due to return to the pharmacy. They do not show up on time. We know this, and we can calculate the number of days late for pharmacy they are as a proportion of the total time on therapy. So this serves as a proxy for their possession of antiretroviral therapy. We converted this proportion into a medication possession ratio, and then divided it into commonly used strata: less than 80-percent, 80 to 94-percent, 95 to 99-percent and 100-percent adherence.

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Now, we also collect information of patient self report. Every time the patient shows up at the pharmacy, an adherence counselor speaks with them. And this counselor asks them how many doses did they miss in the last three days prior to their pharmacy appointment. So we dichotomize this information into any versus none.

Here's a description of our cohort. We have 753 patients who have both viral load information and information on adherence. The median age was 36 years. It's 49-percent male. Low CD4 count, 112 is the median, primary WHO stage 3 and 4, and the median time on therapy was 694 from initiation of ART until the first viral load.

Now, when you look at these characteristics broken down by the adherence categories, none of them were significantly different with the exception of the presence of adherence support. 76-percent of the patients who were in the 100-percent adherence category had adherence support, whereas less than 70-percent had adherence support in the other categories.

This shows the percentage of patients in each category of the MPR who have suppressed viral loads. So, in the 100-percent, 75-percent of the patients are suppressed, and then 95 to 99-percent, 72-percent of patients are suppressed. Then it drops off down to 63-percent in the 80 to 95 range, and then

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patients with an MPR less than 80, 53-percent of those are suppressed.

This shows the relative risk of detectable viral load by the medication possession ratio. With 100-percent being the reference, patients who are in the 95 to 99-percent category are roughly about the same as the patients in the 100-percent category. However, when you move down to the 80- to 94-percent, you get about a 50-percent increase risk of having detectable viremia. And patients in the less than 80-percent category are roughly twofold increased risk of having detectable viremia. This dose response relationship persists when you adjust for baseline CD4, adherence support and age.

Now, when you look at the relative risk of detectable viremia by self reported missed doses, you really don't see a relationship here. Patients who reported missing any dose: very few of them, only 181. 63 of those had detectable viremia with a relative risk of roughly 1.1, so there's no relationship.

I think there are some strengths to our study, because the simple measure of the medication possession ratio, which it may overestimate adherence, I don't think it does so as grossly as other common or cheat methods used in the developing world, such as patient self report. This study represents the real world operational context of the large scale public health

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program. And the viral load data analyzed [inaudible] rationing strategy utilized in clinical care in resource poor settings. However, there are also limitations. Both of these adherent measures are only surrogate markers for true adherence, where true adherence is probably going to be difficult to determine in this large scale resource poor setting.

These results may not be generalizable because they're based on viral loads that are not routinely ordered. These are targeted indicated viral loads of patients who are possibly failing based on clinical immunologic criteria. And finally, there's no confirmatory load, as this represents just one viral load done at a point in time. We didn't have the resources to confirm there.

So, in conclusion, adherence based on pharmacy refill data predicts virologic failure, and it shows a nice dose response relationship, whereas self reported missed doses does not appear to predict virologic failure.

I'd like to acknowledge the Zambian ministry of health, the Lusaka Urban District Health Management team, my co-authors and collaborators, and last, but certainly not least, the patients. Thank you.

[Applause]

**JAVIER R. LAMA, M.D., M.P.H.:** Thank you, Dr. Cantrell. Questions from the audience, please? So, microphone number two, please, and then one?

**MALE SPEAKER:** Hi. I've heard the adherence support marker as being important in a lot of other studies, and reported a lot in the literature. I'd be interested in your impression. My impression is that adherence support isn't necessarily what improves adherence, but the lack of having adherence support and disclosure is a marker for a barrier to adherence, like depression or social isolation. And I was just curious. I haven't really seen a randomized trial to look at disclosure and the impact of disclosure on adherence. I was just curious what your impression was.

**RONALD CANTRELL, M.P.H.:** That's a very good point. And I would tend to agree with you. I think that it does represent more of a barrier. But I don't know if we have the data right now to answer your question, like a study would be a good idea.

**MALE SPEAKER:** My thought might be that people who don't have adherence support, if they were forced to disclose to someone, they might not have improved adherence, because of not disclosing because of some other reason.

**RONALD CANTRELL, M.P.H.:** Right. And we don't collect that information. It's just a simple question on their initial

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history and physical, if they have someone that they've told. So we don't get more specific. But that's a very good point.

**MALE SPEAKER:** I mean, what it might do is it might identify a population of individuals who don't have adherence support who might need more intensive adherence intervention.

**RONALD CANTRELL, M.P.H.:** Thank you.

**JAVIER R. LAMA, M.D., M.P.H.:** Microphone number one, please.

**MARK BOYD:** Yes. Mark Boyd [misspelled?], Australia. I think in your conclusion, you showed us a slide that said that the medication possession calculation if you like that you used was a good predictor of virological failure. But in fact, in your presentation, what you presented were the various relative risks according to odds ratio, depending on the strata. And I just wondered whether, in terms of prediction, you actually had done any calculations of positive predictive and negative predictive values based on what you presented.

**RONALD CANTRELL, M.P.H.:** We did not do that analysis. And that's a very good point. We'll look into that.

**JAVIER R. LAMA, M.D., M.P.H.:** Number two, microphone number two.

**JOHN ZIEGLER:** John Ziegler [misspelled?], Sydney. Are you able to tell us how much of the virological failure can be

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explained by the problems with adherence that you've identified?

**RONALD CANTRELL, M.P.H.:** Can you be more specific?

I'm sorry.

**JOHN ZIEGLER:** Well, if you looked at it the other way around, patients with virological failure, how many of those appeared to be fully adherent. So, how much of the virological failure is in fact an adherence problem?

**RONALD CANTRELL, M.P.H.:** Well, I mean -

**JOHN ZIEGLER:** Clearly adherence is a big part of it, but is it enough to explain it all?

**RONALD CANTRELL, M.P.H.:** Well, it explains it - the only other predictors of virologic failure were the CD4 count and age and presence of adherence support. But even after adjusting for those, the MPR still predicted having virologic failure.

**JAVIER R. LAMA, M.D., M.P.H.:** We have time for the last question. Microphone number one.

**MALE SPEAKER:** Tal [misspelled?] from P&G. I'm just wondering whether other variables such as geographical location and whether patients have enough money to come to the clinic and so on and so forth. I know these probably were not addressed here, but do you want to make some comments in that regard, please, regarding adherence? Thank you.

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**RONALD CANTRELL, M.P.H.:** Well, the population in Zambia is pretty uniform. It's primarily lower income patients. So we don't have the socioeconomic information you're asking about. But most of the patients present in the same strata. Does that answer your question?

**JAVIER R. LAMA, M.D., M.P.H.:** Thank you, Dr. Cantrell.

[Applause]

**JAVIER R. LAMA, M.D., M.P.H.:** The last speaker of this session is Dr. Paula Munderi. Dr. Paula Munderi is the head of the HIV clinical research program in the MRC Research Unit [inaudible] AIDS of the Uganda Virus Research Institute. She will talk about these programs [inaudible] biological, immunological and clinical outcomes at 48 weeks in a randomized comparison of ZDV, 3TC and NVP and ZDV, 3TC, ABC in 600 patients with low CD4 counts in Africa.

**PAULA MUNDERI, M.D.:** Thank you very much. And I would like to thank the conference organizers for allowing us to come and share these data.

The NORA study was a randomized double blind placebo controlled 24 week trial, in which we randomized 600 ARV naïve adults with symptomatic HIV infection, CD4 counts below 200 and no other contraindications to ART in a one-to-one ratio to receive either zidovudine and lamivudine, co-formulated as Combivir two times a day, plus 300 milligrams Abacavir and

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[inaudible] placebo, or 200 milligrams of nevirapine and Abacavir placebo. Active nevirapine and nevirapine placebo were given once a day for the first two weeks, and dose escalated at this stage in the usual fashion.

All patients were switched to open label active drug at 24 weeks, and then followed up according to their randomized allocation. The primary end point for this sub-study was safety as defined by serious adverse reactions to blinded Abacavir therapy.

The baseline characteristics are comparable in the two groups. Two thirds of the patients are women, and the median age is about 37 years. The median CD4 count is 99 overall, but by design in this trial, a randomization was 25 by CD4 count about or below 100. About two thirds were at least at WHO clinical stage 3, and baseline viral loads are quite high in both groups.

A look at the safety outcomes at 23 weeks: 289 patients in the Abacavir arm and 280 in the nevirapine arm completed 24 weeks of treatment. The safety outcomes show the trend towards the lower rate of serious adverse reactions, most of them hypersensitivity reactions in the Abacavir arm, a lower rate of discontinuation of therapy for adverse events with Abacavir, and a lower rate of [inaudible] for adverse events with Abacavir.

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Efficacy analysis was not planned as part of the Nora [misspelled?] study protocol. But because the patients continued to be followed up in the study clinic every four weeks, we are presenting here an exploratory intention to treat analysis of efficacy outcome at 48 weeks. We're considering clinical events, WHO clinical events and WHO full clinical events and death. All of these were documented and independently reviewed.

CD4 cell count was measured in real time, at baseline and every 12 weeks after that. And plasma viral load was assayed retrospectively at 0, 4, 12, 24 and 48 weeks. The rate of lost to follow up was 2-percent, representing 12 patients.

At 48 weeks, 62-percent of the patients in the Abacavir arm had a viral load below 50 copies, compared to 77-percent on the nevirapine arm, a difference of 15-percent. 75-percent of the patients on Abacavir, compared to 87-percent of the patients on nevirapine had a viral load below 400 copies, a difference of 12-percent. Both differences are significant in favor of nevirapine. The mean increase in CD4 cells at 48 weeks was 147 with Abacavir compared to 173 with nevirapine, also a significant difference in favor of nevirapine.

For all the clinical end points we assessed, however, we saw a trend towards superiority in favor of Abacavir. There were 16 deaths with nevirapine compared to 9 deaths with the

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Abacavir combination. Combined WHO 4 clinical events or death were 32 with the nevirapine combination compared to 24 with the Abacavir combination. And combined WHO stage 3 or 4 or death were 48 with Abacavir compared with 68 with nevirapine.

So, this showed some sort of a disconnect between clinical outcomes and CD4 response and viral load. We've considered the following explanations for this apparent disconnect. Firstly, did the increased toxicity of nevirapine account for the excess clinical events? This is unlikely because most clinical events were not related to ARV toxicity but HIV related. Nor was there a difference between the two arms in the rate of switching to alternative regimens, which could possibly have had altered potency, accounting for the viral load superiority, because more ART substitutions were recorded in the nevirapine arm. These differences could, however, be a chance finding and this cannot be ruled out.

We also found no evidence to support the hypothesis that the excess clinical events in the nevirapine arm were due to the immune reconstitution inflammatory syndrome, or IRIS. Although we did not classify clinical events according to whether or not they were IRIS, and this is a limitation, we examined several surrogate markers for IRIS, such as [inaudible] events, the CD4 count and WHO clinical state of

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treatment initiation and the change in viral load at four weeks of treatment.

This table shows the relative risks of combined clinical events between the two groups for clinical events occurring before or after 12 weeks of treatment, and there is no evidence of [inaudible]. We found similar changes for CD4 count and WHO clinical stage at treatment initiation. And we found a similar result for the change in viral load at four weeks.

In conclusion, the nevirapine combination has superior virological and immunological efficacy compared to the Abacavir combination over 48 weeks. However, there is a trend towards superiority of the Abacavir combination in clinical outcomes. No clear explanation so far for this apparent discordance in clinical response versus viral load and CD4 cell response, and this may be a chance finding. However, if this finding is real, it suggests that there's a disconnection between early clinical CD4 and viral load outcomes, and this may influence the way surrogate markers are interpreted.

We thank all our study participants, the patients, and the study staff. Our research is funded by the MRCUK, the Rockefeller Foundation and DFID. And we are grateful, as always, to GlaxoSmithKline, [inaudible] and Gilead Sciences for donation of study drug.

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With your permission, [inaudible] would like to pay a very special tribute to the late Professor Anne McLaren. Professor McLaren died tragically in a car accident early this month. And she has served as chair of the [inaudible] data and safety monitoring committee since the beginning of the study.

[Applause]

**JAVIER R. LAMA, M.D., M.P.H.:** Thank you, Dr. Munderi. Some questions for the audience, please? Microphone number two.

**MALE SPEAKER:** I am [inaudible] from India. We all know that the virological separation is [inaudible] much before the CD4 counts go high, and then that results in clinical benefits. Is this conclusion a function of that sequence of events? First you see viral load separation, then CD4 count goes up, which then translates to clinical benefit. Probably if this cohort is followed up for a longer period of time, then maybe the interpretations can be more meaningful.

**PAULA MUNDERI, M.D.:** Thank you. This is assessment at 48 weeks, and they all [inaudible] simultaneously. So we're looking at [inaudible] 48 weeks, but viral load, CD4 and clinical events within the same period. But we are following up the cohort and will be interested to see if the effects are carried on over time.

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**JAVIER R. LAMA, M.D., M.P.H.:** Okay. Some questions, microphone number one.

**MARK BOYD:** Thank you. Mark Boyd, Australia. Paula, I want to congratulate you and the DART team to begin with, on a really nice piece of trial design and a really nicely conducted study. However, it seemed that in efficacy analyses, you said in one of the earlier slides, didn't actually fall in part of your original protocol plan. And there is a danger, as you pointed out, that when you do post hoc analyses looking at end points that you weren't actually planning the trial around, you stray into the dangerous territory of making type one errors and having chance findings that in fact are simply that. And I thank you for sort of pointing that out.

I guess the question from that is: it was a 600 patient study, and it wasn't clear to me what the actual primary end point was. What was the end point that you were actually examining for which you needed 600 patients? I wondered if you could comment.

**PAULA MUNDERI, M.D.:** Yes, thank you, Mark. I did point out that neuro study design, the primary end point was safety at 24 weeks. And it was actually designed to assess that, safety of Abacavir compared to nevirapine and showing the results of the safety analysis.

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And you're right, it was not powered or designed as an efficacy analysis, but we are looking down stream because the patients maintained their randomized allocations.

**JAVIER R. LAMA, M.D., M.P.H.:** Question from microphone two.

**TOM CAMPBELL:** Tom Campbell from Colorado. My question is about the deaths that occurred. What were the most common causes of death in both arms, and was there any relationship between death in either the virological or immunological responses?

**PAULA MUNDERI, M.D.:** Well, to answer the second part of your question, was surprised at the disconnect between deaths and the virologic and immunological responses. And that's part of what we presented. And this is an extra slide which shows the common causes of death, mainly HIV related. And you can look at the distribution between the arms.

**JAVIER R. LAMA, M.D., M.P.H.:** Can you please relate those? They're not being shown, the causes of death.

**PAULA MUNDERI, M.D.:** Okay, I beg your pardon. I thought they were being shown. So, we've got - okay, now they're being shown. Thank you. It's mainly HIV related infections.

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**TOM CAMPBELL:** Back to my first question. So, were people who were successfully virologically suppressed or had greater CD4 cell increases more likely to die?

**PAULA MUNDERI, M.D.:** That was a surprising finding. They were not more likely - they were more - no, they were not more likely to die. That was a surprising finding.

**JAVIER R. LAMA, M.D., M.P.H.:** Okay, a question from microphone two, Dr. Jeron [misspelled?]

**JOE JERON:** Yes, this is Joe Jeron [misspelled?] from [inaudible]. I'm just trying to follow up on Tom's question. So, specifically, of these 27 patients that died, how many had virologic suppression and how many had a response in CD4 cells?

**PAULA MUNDERI, M.D.:** I'm afraid I cannot answer that question specifically. I do not have that data, but I can probably look it up and tell you. I apologize for that.

**JAVIER R. LAMA, M.D., M.P.H.:** Thank you. Last question from microphone number one.

**IAN FLEMING:** Yes, Ian Fleming [misspelled?] from Copenhagen. I want to also congratulate you on a very interesting but also very surprising finding in a study that was not designed for the outcome that you're assessing. And I appreciate the exploratory nature of the analysis. My question to you is: what will be your next step? This is potentially an extraordinarily important finding if it is to be confirmed. Do

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you already know, decide how you want to move this research question forward?

**PAULA MUNDERI, M.D.:** Well, thanks again. As you have correctly pointed out, you know, the powering at design and the limitation of that. We're following up the patients long term. By now the median follow up is three years plus. And we are looking at the progression of the time and the responses of the time to see if these differences are in fact maintained. We're also doing retrospective analysis of the genotypes among the patients who have had virologic failure. Needless to say, or the patients who fulfilled protocol criteria for failure or regimen failure have been switched to a more effective regimen.

**IAN FLEMING:** I would just offer the suggestion that to repeat this study with appropriate power for clinical outcome, because if it is confirmed, that would - it appears to have major implication for how we think about using treatment. So I would just encourage that. So whatever funding agent is sitting in this room, to go ahead and fund such a study.

**PAULA MUNDERI, M.D.:** We continue to look. We continue to record the clinical outcomes. It will be interesting to look at 96 weeks and beyond, whether these differences are maintained. Thank you.

**JAVIER R. LAMA, M.D., M.P.H.:** Please, very quick question from microphone number two.

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**MALE SPEAKER:** [Inaudible] in developing countries.

[Inaudible], and how many of them may have received single dose nevirapine, because that mean some operative failure or-

**PAULA MUNDERI, M.D.:** Yes. Well, you're right in that two thirds of the treatment population are women, 67-percent are women. We did look at - we do collect data on how many patients have had prior exposure to ARVs for prevention of mother to child transmission. The percentage is extremely low.

**JAVIER R. LAMA, M.D., M.P.H.:** Thank you. Thank you, Dr. Paula.

[Applause]

**LERATO MOHAPI, M.B.B.C.H.:** I'd like to thank all the speakers, my co-chair and the audience. This session is now closed.

**JAVIER R. LAMA, M.D., M.P.H.:** Thank you.

[END RECORDING]