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**4th IAS Conference on
HIV Pathogenesis, Treatment and Prevention
TB/HIV: Still a Deadly Partnership
International AIDS Society and
Australasian Society for HIV Medicine
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GERALD FRIEDLAND, M.D.: Good morning, ladies and gentlemen, colleagues, I welcome you to session MOAB1, TB and HIV, Still a Deadly Partnership. I'm Dr. Jerry Friedland from Yale University, School of Medicine. My colleague, Jose Miro, from the Hospital Clinic, University of Barcelona, will co-chair this session.

I think that the issue of HIV and TB is as large as this auditorium and I'm very excited that we have the opportunity to have an abstract driven session on the intersection of these two extremely important epidemics.

The first paper will be presented by Dr. J.H. Elliott and colleagues from Australia, Cambodia and the United States, entitled Tuberculosis-Associated Immune Restoration Disease is Associated with Increased PPD-Specific T Cell Responses Detected by a Whole Blood Interferon on Gamma Release Assay.

JULIAN H. ELLIOTT, M.B., B.S., F.R.A.C.P.: Thank you everyone, so the aim of the study that I'm going to present today was to investigate immune reconstitution inflammatory syndrome or, IRS, in a setting of high incidences of tuberculosis. In particular, it's incidence, characteristics, and outcomes, it's immunopathogenesis and the performance characteristics of simple tests for diagnosis. We conducted a prospective, single-site cohort study at the National Center

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for HIV/AIDS, Dermatology and STD Social Health Clinic and Ambulatory Clinic in Phnom Penh, Cambodia. We enrolled antiretroviral [inaudible], HIV positive adults and followed them for 24 weeks from the time of ART initiation. At pre-ART, at weeks 4, 12, and 24, we performed the quantifier on TB gold in tube assay using the standard Id1 antigen Neil Tube and positive monitoring control with the addition with a [inaudible] containing PPD antigen. All the results were analyzed as continuous variables following the subtraction of the Neil Tube result. Pre-ART in weeks 12 and 24, we also conducted skin testing using tuberculin, M-avian tuberculin [misspelled?] and candor and trichocyst anagen as an antigen panel. Today I'm presenting the results of preliminary analysis including all participants who completed follow up by the 31st December, 2006. The case definitions for TB RS that we used in this study contributed towards, and are completely consistent with those definitions recently proposed by the International Network for the Study of HIV Associated IRS. In particular a paradox called TB RS is defined as the development of active TB using standard WHO definitions. Our response to TB treatment followed by the initiation of ART and the development of specified manifestations was less than 3 months, subsequently, with the exclusion of other causes. Incident TB on ART is defined as the initiation of ART following the

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exclusion of active TB and subsequently the development of active TB with a subset of incident TB IRS, splitting that group in which specified manifestations developed less than 3 months following the initiation of ART.

The results: 54-percent of the [inaudible] male, the median age was 33 years, baseline WHO stage was stage 3 or 4 in approximately 80-percent of participants. The median baseline CD4 count of 61 and 44-percent had a CD4 count of less than 50 prior to ART. There were 53 episodes of TB in 46 participants and approximately 60-percent of participants, there was overlap between ART and the treatment of TB. 27 participants started ART during TB treatment and 6 started TB treatment during ART. The site of TB in those that developed TB following enrollment in the clinic were roughly evenly split between pulmonary and extrapulmonary sites. The pulmonary cases were split evenly between those that were smear positive and smear negative. 68-percent were treated as category 1 and 15-percent as category 2.

The 155 participants were initiated ART, 27 or [inaudible]-percent started ART during TB treatment and of the 6 of 22-percent developed paradoxical TB IRS. Of these, three required no treatment, two were treated with pernisilan [misspelled?] and one died. Of 128 of the 83-percent participants that started ART not during TB treatment, 6, or 5-

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percent, went on to develop incident TB on ART. Both univariate and multivariate analyses products cultivability IRS was associated with WHO stage 4 disease and there's a trend towards association with low baseline CD4 count and earlier initiation of ART. Restricting this analysis to the participants that started ART during TB treatment, there were trends towards association, again, with WHO stage 4 disease, a low baseline CD4 count and earlier initiation of ART following the initiation of TB treatment.

I'm discussing the results of the analysis, the diagnostic tests; first consider the group in which ART was initiated during the treatment of active TB. In this group, interferon gamma production in response to RD1 antigens was not different between the group that developed paradoxical TB IRS and those that did not. Neither pre-ART or at weeks 4, 12, or 24. Interferon gamma production in response to PPD antigens in contrast, increased in both groups, those who developed paradoxical TB IRS and those who did not. But, there was a more marked increase in the TB IRS group and at week 4, the difference between the groups were borderline significantly different. Similar responses were seen with tuberculin skin testing with increases in both groups, but no significant differences between the 2 groups at any time point.

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Now considering the group of participants who initiated ART not during the treatment of active tuberculosis, in response to Id1 antigens, interferon-gamma production was significantly higher in the group who subsequently went on to develop incident TB on ART compared to those who did not pre-ART. At week 4, in this group, there was a significant increase in interferon-gamma production response to Id1 antigen and a subsequent fall over for weeks 12 and 24, but this remains significantly higher than the interferon-gamma production seen in the group who did not develop TB on ART. In response to PPD antigens, interferon-gamma production increased in both groups but the increase was more marked in the group who developed TB on ART and there's significant difference between the two groups at week 12 and 24. Similar results were seen with the use of tuberculin skin testing, with again, increasing both groups, but a more marked increase in the group with incident TB on ART, with significant difference between the two groups at week 12 and 24.

In conclusion, this study has shown a incident of paradoxical TB IRS of 22-percent in the first six months of ART, when treatment was initiated during TB treatment, with trends towards association with WHO stage 4 diseases, low baseline CD4 count and earlier initiation of ART. Also shown an early, rapid increase in interferon-gamma production

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measured by quantifier on TB gold in [inaudible] assay in participants with paradoxical TB IRS in response to PPD, but not Id1 antigens. There was also an association between the development of incident TB on ART an increase on interferon gamma production measured by quantifier on TB gold in [inaudible] assay in response to Id1 antigens, pre-ART and in response to both Id1 antigens and PPD during early ART and similar responses were seen with PPD skin testing. These preliminary analysis suggest that whole blood interferon-gamma release assays may have a role in the differentiation of paradoxical TB IRS from other causes of clinical deterioration during early ART, and in the prediction and diagnosis of early incident TB on ART

I'd like to thank all the study participants, the Australian Agency for International Development, who funded this study, my colleagues at the National Center for HIV/AIDS, Dermatology and STDs, The National Institute of Public Health in Cambodia, [inaudible] is at the University of Western Australia, my colleagues at National Center and HIV Epidemiology and Clinical Research at the University of New South Wales. Thank you.

GERALD FRIEDLAND, M.D.: Thank you. We have time for several questions. I'd like to actually ask a question about the one patient who died, who was in the paradoxical immune

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reconstitution group, was that death thought to be due to immune reconstitution or what, because we always worry about immune reconstitution is very serious, but usually not a fatal event and always gets factored into the discussion as to when to start because of the seriousness of it, but then, so was that an IRS death?

JULIAN H. ELLIOTT, M.B., B.S., F.R.A.C.P.: Yes, I agree. I think that I would agree with Jerry, it's very important to understand that in most situations, the development of TB IRS is not associated with mortality. In this specific case, the person had developed TB meningitis and then had a very rapid deterioration with death at another hospital, but it was clearly documented as to be due to that meningitis and was so thought to be a manifestation of TB IRS.

GERALD FRIEDLAND, M.D.: Please identify yourself and your institution.

JULIAN ANDREW COBB: Julian Andrew Cobb from [inaudible] here in Sydney. I suppose from a clinical prospective, using a PPD assay, like you see, to predict incident TB or to predict IRS, you'd want to sort of turn the positive and negative predictive values of the test. Have you looked at that?

JULIAN H. ELLIOTT, M.B., B.S., F.R.A.C.P.: Yes. Perhaps, if I can go to the slides, I've just got one

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indicative example of the analysis. I think it's important to realize this is a preliminary analysis and the number of cases are relatively low, once we have the final data set, then we will, of course, be doing all those analysis looking at both products on TB IRS and incident TB on ART. As an example in the group who were developing TB, it will take too long to click through, but at month 1, in the group who had not active TB at the time of initiation of ART, then the performance characteristics of the qualifier on TB gold using Id1 antigen tube, performed quite well. The sensitivity was perfect, the specificity was around 97-percent and predictive values, again, were quite high. I think at this point, with this preliminary analysis, there is at least, the suggestion that these tests might be used in the diagnosis either of paradoxical TB IRS or incident TB on ART.

MANUEL VADECA: Manuel Vadeca [misspelled?] [inaudible] Switzerland, how early was ART initiated in the 6 who had IRS and in the other ones who didn't have. Was that within days or weeks of tuberculous treatment?

JULIAN H. ELLIOTT, M.B., B.S., F.R.A.C.P.: Overall the median time between initiation of the TB treatment and the initiation of ART was around 60 days. In the group who developed TB, paradoxical TB IRS, that very was slightly less, but as I showed in the analyses, there was a trend towards the

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association but it was not significantly different. If you look at just the raw numbers, 4 of those 6 had initiated ART within the first 8 weeks and 2 had initiated ART sometime afterwards.

MALE SPEAKER 2: I have a question for you. In order to study T Cells specific immune responses are [inaudible] what do you recommend to use the PPD antigens or the other antigens because also in a British/French studied this year and [inaudible] any type of specific response, again with two antigens [inaudible].

JULIAN H. ELLIOTT, M.B., B.S., F.R.A.C.P.: Yes, so I think, I think at this stage, the understanding of the pathogenesis of TB IRS is, and everyone will agree, quite limited. And so, in the design of cohort studies, I think we should include as much robust immunology as we can and we should use all available techniques and antigens to study both groups. I think that, as you mentioned, our results are consistent with what Britichal [misspelled?] Transcript has shown that in the products of the TB IRS group, that the interferon-gamma response is predominately seen in response to PPD antigen and now to the Rd1 antigen such as [inaudible] and so I think in the study of that group, then obviously, we need to dissect further out what are the specific components of the PPD that are precipitation that response. In the other group,

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in the group that are developing TB ART, I think we need a lot more work to dissect out the different subgroups. I think most of us feel that there's a large subgroup that is actually a form of IRS and I think that these results tend to support that in that, the responses that we're seeing, in response to the Rdl antigens, are quite different than what I was beginning to be reported in patients with TB who followed during TB treatment. Again, the literature is reasonably inconsistent, but in the use of the quantifier on TB gold test, in general, during TB treatment, is a reasonably stable level of response on interferon-gamma response, although there's a bit of noise, there's a lot of variation during that and I think [inaudible] published that recently from the cohort in India.

What we're seeing here is a much more consistent response. We see very high levels initially and then a tiling off. I think that tends to group, at least a large portion of this group, of developing TB during [inaudible]. There's a large component of the immune response that's involved with that. Now whether that's an association, it's not cause and effect, whether this is TB that would have developed otherwise and you are seeing your robust immune response because of the ART or vice versa, you're getting a robust immune response and therefore developing the clinical manifestation. We need much more research to show it.

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GERALD FRIEDLAND, M.D.: Thank you Julian, excellent presentation. [Applause]

Next paper will be presented by Dr. Avihingsanon and colleagues from Thailand and the Netherlands, 24-Week Efficacy and Safety of Nevirapine; 400 mg Versus 600 mg Based HAART in HIV-infected Patients with Active TB Receiving Rifampicin.

ANCHALEE AVIHINGSANON, M.D.: Good morning, I would like to thank you [inaudible] to allow me to present this study on behalf of my colleague.

Rifampicin is a strong and there's a [inaudible] for 50, the combination of ART and Rifampicin that can be used to get are easily needed. If [inaudible] space regimen is compliment with Rifampicin, in case, allergy, toxicity, pigments, and [inaudible]. However, nevirapine can be an alternate option. [Inaudible] those combinations with [inaudible] and RTY are highly used in recourse in [inaudible] cut settings where TB is common. In compliment that with Rifampicin the nevirapine levels are reduced by 20 to 50-percent. [Inaudible] a need of a dose in nevirapine then compliment that with Rifampicin is unknown, especially in Thia populations where European [inaudible] is higher than Caucasian. Applying a higher dose of nevirapine may prevent the [inaudible] of [inaudible] nevirapine levels, but they also induce more liver toxicity. Because [inaudible] interactions,

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the appropriate dose of nevirapine is unclear. Nevirapine trial, looking into to optimal dosing of Nevirapine in these populations are lacking. Why we would like to investigate whether in Rifampicin treated patients, nevirapine has to be increased to 600 mg per day and to assess whether [inaudible] 200 mg q.d. is appropriate during the first two week period and to assess the safety and tolerability of European company that's just Rifampicin. So this is the prospective when Rifampicin, [inaudible] in five sites in Bannock and [inaudible] in Thailand. Our populations were HIV [inaudible] our TB smear positive, CD4 less than 200 and taking Rifampicin [inaudible] for 2 to 6 weeks. These patients were [inaudible] and higher dose nevirapine at [inaudible]. The backbones of ACT and [inaudible] so we used to fit those combinations, ACT to 50 mg and [inaudible] and nevirapine [inaudible]. Doing that 14 days, in both groups. So first group lead in with nevirapine 200 mg q.d. and the second group lead in with nevirapine 200 mg bid. The [inaudible] will compare [inaudible], you can see they were very advanced patients, with low CD4 and high [inaudible] The majority of them [inaudible] they have low hemoglobin at the baseline. The nevirapine, at minimum concentrations at week 2, week 4 and week 12. The blue colors show the European [inaudible] and the red triangle show the [inaudible], as you can see, the level in arms 1 is

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typically lower when compared to arm 2 at week 2, and the level was increased at week 4 and was still lower than arm 2. The level was comparable with 12. You can see that the [inaudible] had higher [inaudible] from week 2 to week 1. About 80-percent of patients in arm 1 has some [inaudible] in nevirapine when compared to arm 2. [Inaudible] and at the end period at week 4 and week 12, the [inaudible] were comparable.

We have two case deaths, one from [inaudible] and one from [inaudible], and 25-percent of patient [inaudible] required by transfusion during the first three months. Also, have about 30-percent that [inaudible]. The TB [inaudible] was the most common TB IRS. We had one serious case with [inaudible] required emergency drainage.

The ART [inaudible] were comparable [inaudible]. In group 2 we have more cases with hepatitis C co-infections and higher ALT baseline. So from a [inaudible] both of them were hepatitis B and hepatitis C co-infection. Look at the hemoglobin in [inaudible] overtime after treatment of tuberculous and HIV.

The Rifampicin, about 50-percent of patients had rifampicin and [inaudible] and 80-percent in arm 100-percent in arm 2 had [inaudible] at 24 weeks. The CD4 response has tend to have a higher CD4 response in arm 1, 100 cell with 40 cell in arm 2.

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In nevirapine [inaudible] treated patients, up to 80-percent of patients in nevirapine has an optimal level at 2 weeks [inaudible] nevirapine hypersensitivity. Based on this multiple site study, at 24 weeks by [inaudible] the rifampicin was similar between the two groups. IRS [inaudible] patients when HAART was commenced within 2 to 6 weeks up to [inaudible] treatment. The [inaudible] best regimen in early, first three months of our tuberculous, HIV/TB patients [inaudible] higher infusions require [inaudible]. So, nevirapine [inaudible] or higher dose of nevirapine is not recommended due to a higher risk of nevirapine association hypersensitivity. Although, up to 80-percent of patients in the stand out in both groups, has some optimal level at 2 weeks, [inaudible] compared between 70 patients with rifampicin and 30 patients without rifampicin has shown that the nevirapine [inaudible] they may be sufficient for most [inaudible] for patients receiving rifampicin.

On this, preliminary data analysis, the SMB subset that nevirapine higher dose choose not be further investigated so our study was prematurely terminated. Our [inaudible] patients with multiply sites and [inaudible] and nevirapine may have intercepted validity and that's this data [inaudible].

Finally, I would like to thank you for all my colleagues to have [inaudible] contribution to this study. Thank you. [Applause]

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GERALD FRIEDLAND, M.D. Thank you. I have a question. I noticed there's a high rate of study discontinuation among the patients, was that largely related to the AZT enema or was that actually due to the hypersensitivity or the navira type associations and were there a difference in the discontinuation rate between the high and lower doses?

ANCHALEE AVIHINGSANON, M.D.: Yes, so we have four cases with nevirapine hypersensitivity in higher doses and one in lower dose and these patients were, [inaudible] and one died from each group. I also have a [inaudible] come back to be [inaudible]. So we [inaudible].

GERALD FRIEDLAND, M.D.: Questions? I was glad to see that your final point in which you, at least, raised the question as to whether the difference in BMI and admisity might actually, how generalizable this is, I'm think of the presenter and the co-chair and wondering whether we could say a dose of nevirapine we would actually have similar levels.

ANCHALEE AVIHINGSANON, M.D.: Yes, so actually in Thia population, they tend to have a higher level of nevirapine than [inaudible] Caucasians and higher than any ethnicity so why we have higher nevirapine level, and I think, based on this study, if we start with higher dose, we face off the higher risk of toxicity, but if we start with lower dose, [inaudible] at the beginning, we will face off the suboptimal levels, so we have

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to balance between risk and the risk of resistance. I will say that maybe we could go with just only one week in [inaudible] and no further [inaudible]. This may be just a [inaudible]

GERALD FRIEDMAN, M.D.: Dr. Altese [misspelled?].

RICK ALTESE: Rick Altese from the US, I think you began to answer part of my question, but when you have 83-percent of your subjects who have a relatively suboptimal dose of nevirapine during the first couple weeks and it seems to normalize, a couple of questions would be raised. One, do you have any sort of ideotype resistance mutations at 24 weeks, which is relatively short, you have similar efficacy. However, are those folks on their way towards failure at a later point because of the ideotype resistance mutations? Second of all, is there not potentially different approaches you might consider as part of the next study in terms of what dose you use as part of the lead-in dose in nevirapine?

ANCHALEE AVIHINGSANON, M.D.: Yes, for the [inaudible] resistance, we had in only one patient, but that patient, his appearance was very poor and we cannot see any mutations even [inaudible]. All patients are doing fine right now and even the patients who switched from nevirapine to rifampicin had the nevirapine hypersensitive [inaudible].

RICK ALTESE: But what about the ones who are not detectable?

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ANCHALEE AVIHINGSANON, M.D.: That one, we did the resistance testing, we cannot find any major mutations, so we're thinking about [inaudible] because levels still high and cannot take the rifampicin.

GERALD FRIEDLAND, M.D.: Thank you very much.

[Applause]

JOSE MIRO, M.D.: We will move to the next presentation, the title is "TB Co-Infection Treated at Onset of Therapy Does Not Affect Long-Term Risk of Treatment Failure Among HIV-1 Infected Patients Initiating Efavirenz Based Combination Antiretroviral Treatment". The presenter is Dr. Ketan Patel, on behalf of Indian and United States Investigators.

KETAN PATEL, M.D.: Good morning everybody. Today I'm presenting our data on TB co-infections treated at the onset of therapy doesn't affect the long-term risk of treatment failure among HIV infected patient initiating efavirenz based on combination antiretroviral therapy.

As you all know, still, we continue to be one of the commonest infections in HIV infected patients in the developing countries. They are missing a key compound; often due to TB treatment has significant drug interactions. Significant drug interactions along with [inaudible]. It reduces the exposure to efavirenz by [inaudible] which is more marked in individual

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with high body rate. We previously we [inaudible] in AIDS 2004 that, a charity co-infection can be treated by [inaudible] administration of [inaudible] based on HAART without compromising data and efficacy. [inaudible] reported in AIDS 2005 that we [inaudible] comparable among the patients were seeing 600 and 800 mg with [inaudible] by increase to 800 mg by using rifampicin is not necessary and may be associated with increase side effects. But I [inaudible] based treatment the onset of combination ART may have a negative implication despite initial successful [inaudible] constitutions. So, [inaudible] at the start of TB treatment, a long-term response based on combination ART. [inaudible] 9 patients starting on efavirenz 600 mg based on HAART along with cART [inaudible] clinic. Patients with many months of follow up are included in our analysis, those with tuberculous [inaudible] in addition to combination ART and those without tuberculous received only medicines based on combination ART and after 9 months, all patients continued to receive [inaudible] based on combination ART alone. All patients [inaudible] clinic 3 or more [inaudible] then every 3 monthly. CD4 cell count was carried out every month, baseline correct [inaudible] were noted, patients were mostly follow up for any drug interactions and treatment [inaudible] was defined as immunological failure. With this data, we analysis using [inaudible] and statistically

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analysis was [inaudible] 283 subject [inaudible] of more than 12 months on the evidence based on ART of which nearly 51 percent of patients were TB co-infected and near 49 percent of the patients were not TB co-infected. So [inaudible] is similar. This is what they were showing the baseline [inaudible]. You can see the age, the sex distribution and [inaudible] in both TB and non-TB group comparable. How the baseline CD4 count goes a little bit lower in patients with tuberculous and then patients without tuberculous and the [inaudible] was statistically significant in this group. At the end of 9 month, at the end of TB treatment, the difference in the [inaudible] group, as far as CD4 cell count [inaudible] was not statistically significant.

This is a graph showing the CD4 response at [inaudible] point in each group. The blue line represents those patients without tuberculous and the black line represents those patients with tuberculous and below we have given the numbers of the patients in each line bar and you can see that a number of patients in each group, [inaudible] are near equal and the baselines are going fairly parallel and there was no significant [inaudible] except a few hitches in patient with tuberculous and all statistical analysis was [inaudible] and no significant difference as far as the [inaudible] of CD4 bond in both groups are concerned.

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If you look at the [inaudible] data, nearly 62 percent of the patients in TB groups and the 65 percent of patients in non-TB group had a nontypical para regular follow up, 21 patients in [inaudible] and [inaudible] and nearly 6 to 7 patients in TB group and 4 percent in non-TB group [inaudible] to follow up. [inaudible] when compared between these two groups was comparable and there was no statistically significant difference was found.

Later on, treatment was changed to [inaudible] in 7 patients in TB group and 2 patients in non-TB groups because of financial reasons.

[inaudible], at the end of doing this three year follow up, nearly 12 percent of patients in TB group had a failure to treatment when 10 percent of patients in non-TB group had a failure to treatment. All the difference between these two groups as far as failure response was not statistically significant. [inaudible] last patient as a failure, even then, 18 person and [inaudible] in the TB and non-TB group had a failure and the difference was statistically significant even then also.

So, as far as failure was concerned, both groups were comparable.

This is the table showing time to failure in each group. You can see at each point of time, the amount of

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patients failing to the [inaudible] there was no difference as far as failure response.

This is a table showing adverse reaction in each group of patients. You can see, only hepatitis, which is more common in [inaudible] as compared to non-TB group, but incidences like this was nearly 2 percent. Hepatitis in TB group was managed by discontinuation of a paradoxical drug and none of the patients in both the groups required this [inaudible] based combination ART and patients improved by [inaudible]. Side effects, like [inaudible] skin rash, [inaudible] very comparable in both the groups and there was no statistically significant was found.

In the [inaudible] was seen nearly 15 percent of patients in TB grouped and 9 percent of patients in non-TB group and that difference was not significant. None of the patients in TB group had [inaudible] combination ART and none of the patients in non-TB group developed tuberculous while on combination ART.

So in conclusion, the [inaudible] based TB treatment [inaudible] evidence based combination ART [inaudible] or increased the risk of [inaudible] base treatment [inaudible] amount the [inaudible] infected patients over three years of follow. [inaudible], one was selection biased, [inaudible] patients completing 12 months of therapy treatment. Failure was defined by immunologic failure only, we don't have any

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viral load [inaudible] we are not conducting viral load in our patients. Thank you very much for listening.

[Applause]

JOSE MIRO, M.D.: Can you explain please, the reasons of the treatment failure? All were immunological reasons or there were another ones?

KETAN PATEL, M.D.: We have not done viral load in any of the patients and all the patients were failing the study all had immunological failure with clinical failure.

JOSE MIRO, M.D.: How do you define immunological failure?

KETAN PATEL, M.D.: Immunological failure was [inaudible] with change of more than 30 percent absolute [inaudible] failure.

JOSE MIRO, M.D.: Other questions?

MALE SPEAKER 1: Could you define the clinical status of the TB patients at entry. You mentioned they're may have been some selection bias and I saw that the CD4 counts were low, but did they have extrapulmonary disease? Did they have very serious tuberculosis where you would expect the outcome even with antiretroviral therapy, might be problematic?

KETAN PATEL, M.D.: Nearly 48 percent of our patients had lympho [inaudible] at onset and nearly 20 percent of our patients had pulmonary tuberculosis, 7 to 8 percent of our

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patients had [inaudible] disseminations and 2 to 4 percent of our patients had [inaudible] and 1 percent of patients had meningitis with tuberculous. This was the distribution of patients [inaudible].

MALE SPEAKER 2: Mark Boyd, Australia, can you comment a little, doctor, on the people that were lost to follow up, it seemed like particularly over the two years, there was a substantial lost to follow up in your [inaudible] what if it was [inaudible] and actually find out what happened to them, did they in fact die? Or is that not possible.

KETAN PATEL, M.D.: [inaudible] and patients were coming too far. They were coming from 200 or 300 miles away from their house to a clinic and we don't have follow up data what happened to that patient that are taking medicines, [inaudible], what happens, we don't have any data regarding that and as our patients have come too far and they don't have any facilities [inaudible] or any of the ways by which we can contact them, so it's difficult [inaudible] to comment regarding your questions.

MALE SPEAKER 3: If I may, how is coherence measured in these patients? I understand the long term follow up, but how did they attend clinic if they lived so far away? What was the measure of appearance?

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KETAN PATEL, M.D.: Generally we call our patients after [inaudible], patients come every three months and most of the patients are coming every three months. Some patients, which are regular follow up, they come after 5 or 6 months, but they are taking other medicines and this was reflected in the CD4 count and [inaudible].

MALE SPEAKER 3: But were the TB meds administered by directly observed therapy?

KETAN PATEL, M.D.: No, it was not medically observed therapy.

MALE SPEAKER 4: Maury [inaudible] from Singapore. Just two questions, one, I noticed that you used 9 months TB therapy in the study, I was just wondering whether there's any particular factures which made you decide on 9 months rather than 6 months?

KETAN PATEL, M.D.: Generally it is our policy at our clinic that most of our patients are seen [inaudible] so it's our policy at our clinic that we use in all these patients and all the patients, 9 months for follow up therapy.

MALE SPEAKER 4: The second question that I had by me, [inaudible] no uncommon is a patient that is EFV positive and unable to differentiate between disseminate TB and [inaudible]. Sometimes in that scenario we initiate them on [inaudible] in addition to standard TB medications, does you center have any

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[inaudible] about possible [inaudible] with rifampicin and the antiretroviral regimens?

KETAN PATEL, M.D.: Probably we have lot come across any case of [inaudible] so, regarding your questions, we are not using clinical [inaudible] and regarding diagnosis of [inaudible], we have not come across any patients who is diagnosed to have a MAC infection.

JOSE MIRO, M.D.: Next question, a short question and a short answer please.

MALE SPEAKER 5: I am Dr. [inaudible] I am from India. Is the 9 month treatment recommended by the National TB program or is it, [inaudible]

KETAN PATEL, M.D.: No, [inaudible] in which it was, I forgot the name of general, but it was told that immunosuppressed patients, [inaudible] 9 month treatment is [inaudible], but previously we were using because of [inaudible]. [Applause]

JOSE MIRO, M.D.: Next presentation is Incidence of sub-therapeutic tuberculosis drug concentrations and associated treatment outcomes among predominantly HIV-infected tuberculosis patients, ins Botswana. The presenter is Sekai Chideya, from US Center for disease control and prevention [inaudible].

SEKAI CHIDEYA, M.D., M.P.H.: Thank you. Good morning everyone.

Tuberculosis or TB is a life threatening but curable disease caused by *Microbacterium tuberculosis* and is the leading cause of death among people living with aids worldwide. Chemotherapy for TB has been in use since 1946 and current treatment regimens include Isoniazid, rophampin, [inaudible] as the basis of most therapies, yet despite their importance in defining treatment schedules, pharmacokinetic profiles of these medications have typically been established on healthy adults. Lower than expected levels of TB drugs have been reported worldwide and associated with gastrointestinal illnesses, drug/drug interactions, patient demographics and HIV infection, to name a few. Potential sequelae of low TB drug levels include poor TB treatment or responses such as prolonged symptoms with infectionness; treatment failure and death; and perhaps more importantly, the development of drug resistant *Microbacterium tuberculosis*. Given this, we think it is very important that population specific pharmacokinetic norms be established for those for whom they are relatively unknown and whom make up the majority of cases in the TB epidemic today. Mainly people living with HIV and AIDS and sub-[inaudible] Africans. And, the [inaudible] that is drug resistant, or XDR TB medicated a pressing need to reassess the pharmacokinetic

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parameters of TB drugs worldwide and how they affect patient outcome which is something that few studies to date have done. Given this, the objectives of our study were to determine the frequency of low serum levels of ionized, [inaudible] among adults with TB in Botswana. We also sought to identify associations between patient risk factors and low drug levels and to investigate associations between low drug levels and poor outcomes.

This flow chart outlines our study methodology. All patients attending [inaudible] largest outpatient clinic were invited to participate in this study if they were of age over 18 years, 18 years or older, complained of cough for two or more weeks, had an abnormal chest x-ray, agreed to HIV testing, had a positive sputum AFB smear or bacterial culture and had imitated TB treated in the past 7 to 13 days. Those who gave consent were enrolled and then hospitalized where they were kept fasting for at least 8 hours. After 8 hours or more of fasting, all four study drugs were administered simultaneously and serum was drawn at 1, 2 and 6 hours after dosing. Specimens were then frozen and shipped to a US laboratory that specializes in drug level analysis. Patients were then discharged and continued TB treatment on an out-patient basis. They were asked to return for clinical evaluations at 2, 6, 12, and 18 months after treatment initiation.

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For this study, we defined low maximum serum drug levels, or Cmax using the previously published referenced points listed here. We considered a patient to have had a poor treatment outcome if he or she had either treatment failure or had death during treatment. We defined a treatment failure in one of two ways. Having either sputum that was positive after 6 months of treatment on AFB smear, or for those patients for whom 6 months smears were not done or not available, having no clinical improvement after 6 months of treatment.

Data analysis is involved in two steps. First we preformed [inaudible] of risk factors versus our treatment outcome variable. Second, we preformed a logistic regression of the poor treatment outcome variable against risk factors having a P value less than 0.1 on our unvaried analysis. Exact methods were used for cell sizes less than 5 patients. 442 patients were screened for enrollment in this study. Of these, 192 were excluded because they did not meet one or more eligibility or exclusion criteria. Of the 250 patients enrolled, 25 were excluded from our final analysis because of missing data or non TB growth on cultures. Therefore, our final sample size included the 225 patients in the analysis. This table lists some of the important characteristics of those 225 patients. Of note, 69 percent were infected with HIV; none of those living with HIV were taking antiretrovirals; the

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median CD4 count of all patients was 269 cells per microliter, however, among those who were infected with HIV the median CD4 cell count was 189. Because of previously literature linking low TB blood levels with both HIV infection and degree of immunosuppression, I will be presenting data on drug levels and treatment outcome stratified by both HIV infection status and CD4 count. A CD4 count of 200 was used as a cutoff because of its AIDS defining significance as well as because of its proximity of the median CD4 count of our HIV infected population. No patient who was not HIV infected had a CD4 count below 200.

This table describes median Cmax values by HIV and CD4 status. Of note, Cmax values of both rifampicin and pyrazinamide different significantly by HIV and CD4 status. Applying the previously mentioned definition and as we found a considerable proportion of patients had low levels of TB drugs, particularly rifampicin rifambutol and isonid. Additionally, among patients who were infected with HIV, those who had CD4 counts 200 or less, were significantly more likely to have lower rifampicin levels than those who had CD4 counts greater than or equal to 200. Similarly, the risk of death during treatment and overall poor treatment outcome were significantly higher among those who were both HIV infected and those with lower CD4 counts. Risk of treatment failure was not

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statistically significantly associated with HIV or CD4. After [inaudible] analysis, three risk factors, being HIV infected, having a CD4 count less than 200 and having pyrazinamide low were significantly associated with the risk of poor treatment outcome. When these three risk factors were entered into our logistic model, only CD4 count less than 200 and [inaudible] remain significant.

Looking more closely at parazimide and individual treatment outcomes. Low parasiticide was associated with both risk of treatment failure and a death during treatment, even after controlling CD4 count and HIV infection status.

There are both strengths and limitations to our study, which we acknowledge. Some strength include that this was a prospect cohort study that had a relatively large sample size compared to other pharmacokinetic studies. However, there was a high mortality rate among out study population and autopsy were not commonly performed in Botswana at this time. Additional, pharmacokinetic testing was only preformed once during out study and we realize that pharmacokinetic profiles of these patients may have changed as their health status changed.

In conclusion, low TD drug levels occurred frequently in our study population and immunosuppression was associated with some pharmacokinetic operations. Low parasitimid levels

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may increase the risk of both treatment failure and death during TB treatment. We are hopeful that future steps will include establishing TB drugs, pharmacokinetic norms for people living with HIV and AIDS, people of color and women and further investigation will be done as to paradiidymides role in TB treatment, the relationship of TB drug pharmacokinetics and required drug resistance and antiretroviral effects on TB drug levels. Thank you very much.

JOSE MIRO, M.D.: Questions?

MALE SPEAKER 1: Who do you [inaudible] and can you comment something about the [inaudible] tuberculosis [inaudible], they were, the first line TB drugs or-

SEKAI CHIDEYA, M.D., M.P.H.: No, those are two great questions. Let me answer the second question first. We did do some cultures on all of the patients and all of those, the majority who were culture positive, we did do drug sensitivity testing. There were only two patients who had multi drug resistance. [Inaudible] out of the whole cohort and two additional patients who had mono resistance to rifampicin. Other than that, everyone was [inaudible] susceptible.

In regards to parazidimin role, it was definitely very suppressing for us to see these results and we kept analyzing the data, trying to figure out you know, whether we were confounding it in some way, but no matter how we analyzed it,

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[inaudible] kept coming up as very significant, even though, oddly enough, the frequency of parasidamid being low is the lowest of all four mediations. We're still not quite sure why it may be. My theory is that pyrazinamide, like isoniazid, really takes most of its strength from working in granulomas and more acidic environments and it may, when it's low, prevent TB, the Microbacterium from really being eliminated throughout the body and so people are more likely to continue to be infectious and continue being sick if those, you know, acidic granuloma environments are not really sterilized. As to why pyrazinamide may be the key other than that, I'm not quite sure. We are trying to figure out whatever risk factors can predict [inaudible].

MATT BOYD: Hi Matt Boyd from Australia. Just a couple of questions. One, you showed that your pk parameters for some of the drugs and they differed between HIV infected people, particularly with low CD4, but I didn't really get a feel for how drastically low those levels were, as against, say, a genuinely accepted standard of what, an excepted minimum would be and whether in fact that lever was lower than that accepted minimum.

The other questions is, in terms of outcome, we're these patients reviving TB dots or were they not?

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SEKAI CHIDEYA, M.D., M.P.H.: Yes. They were all receiving TB dots. Directly observed, they were not getting packets of medications every week, they actually were getting it daily.

In terms of how low is low, I am using definitions here pharmacokinetic definitions that were established starting in the 60's and that has been validated, but again, validated mainly on healthy people, not on people who are actually suffering with TB. I think, let's see, these are the median values, the definitions, if you see here, you know, are below 3, below 8, below 2 and below 35, so most people were not horribly below, but by definition they were low. There were some people who, as you can see, had median levels or levels of 1.3 instead of 3 so, less than 50 percent where it should be.

MALE SPEAKER 4: Hello, I'm [inaudible] from India. A quick question, maybe I missed the point in your presentation, what was the duration of the treatment for tuberculosis?

SEKAI CHIDEYA, M.D., M.P.H.: Six months was standard treatment as part of the National TB program guidelines. However, it was extended if the person had treatment failure of, you know, any other reason, any other circumstances, but 6 months was the typical—

MALE SPEAKER 4: For both HIV and non-HIV and there was no difference?

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SEKAI CHIDEYA, M.D., M.P.H.: Yes. No difference.

MALE SPEAKER 5: One of the questions was probably answered and that was the TB, the dot program. I was just wondering about it, compliance or adherence. First thing. Secondly were they using a fixed dot combination or a non-fixed dot combination for the TB drugs?

SEKAI CHIDEYA, M.D., M.P.H.: These were not fixed-drug combinations. These were for individual meds, so for individual package meds, not combination pills. These were medications that were [inaudible] by the National TB program. In terms of, I'm sorry; I forgot your first question.

MALE SPEAKER 5: The adherence.

SEKAI CHIDEYA, M.D., M.P.H.: Adherence. Yes, we looked at the number of doses of dots received during the study period between HIV infection status by CD4 count and there was no significant difference. The median number of doses that were received was 186 doses.

MALE SPEAKER 5: Should we consider in the future TB treatment with high dose of pyrazinamide?

SEKAI CHIDEYA, M.D., M.P.H.: I think for some of the medications, that would not be a bad idea, those that have not been shown to have significant toxicity if you increase the doses such as rifampin. For other medications, I think, you know, it really needs to be taken into consideration, the

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balance between toxicity and improved efficacy. I think that it's a little bit more complex than just increasing the doses of these medications. I think we need to sort out why some of these people are having these pharmacokinetic apparitions and whether they actually clinically significant. If you look at this, over 80 percent of people, regardless of their HIV infection status, had low rifampin levels, but we know that 80 percent of these people did not have poor treatment outcomes, so I don't think it's as cut and dried as looking at the levels. We want to, kind of, put out there for other researchers is maybe more observation and determination of pharmacokinetic parameters should be done so we can have a better, larger body of knowledge and evidence from which to see what's important, what's not.

MALE SPEAKER 6: This question is concerning the definition of full outcome. You accept that full outcome of TB when the patient develops a clinical configuration but you did not require micro immunological information of TB so the question is, how you can differentiate that the full outcome of TB as opposed to [inaudible] of HIV infected AIDS.

SEKAI CHIDEYA, M.D., M.P.H.: No, you are absolutely correct, I guess you mean in regards to the treatment failure, the second definition of treatment failure? We were torn about extending the definition of treatment failure to, kind of a

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more, clinical versus a laboratory definition, but I think we realized, and something I realized as a clinician myself is that if you see someone coming into your clinic and they are still symptomatic, in a way that potentially could be tuberculosis but you don't know if it's tuberculosis or PCP or some other kind of community acquired disease, pneumonia, most likely that clinician or provider is going to treat the person as if they still have TB and they're going to continue them on TB medications. Unfortunately, most providers in Botswana don't have the luxury of doing laboratory confirmation every time a patient comes in and they're not better. So, this is mainly a clinical definition based on what we thought the providers would do if a patient like this came in.

JOSE MIRA, M.D.: We don't have time for more questions, we must move to the next. Thank you very much.

[Applause]

The last presentation is mortality associated with tuberculosis in HIV positive and negative patients in the HAART era, in Rio de Janeiro, Brazil and it will be presented by Dr. Rolla. Thank you.

VALERIA ROLLA, M.D.: Ladies and gentlemen, I'm glad to be here and to present you the results of our study, mortality associated with tuberculosis in HIV positive and HIV negative patients in the HAART era, in Rio de Janeiro, Brazil.

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Your objectives of this study, which compared tuberculosis mortality between HIV positive and negative patients and to analysis variables associated with tuberculosis staph. This is a prospective cohort study conducted at [inaudible] Referral Center at [inaudible] from January 2000 to August 2006. Follow up was censored one year after the end of tuberculous therapy. The inclusion criteria were to have a positive culture, for Microbacterium [inaudible] to start antigen clauses therapy and to agree to participate in the study.

All tuberculous and antiretroviral therapies followed the national recommendation. In united stations, HAART was initiated at least 30 days after the [inaudible] therapy. Multiple drug resistance was defined as resistance at least to rifampicin and isoniazid. Tuberculous associated there well consider it [inaudible] during tuberculous therapy and the other cause were identified. For the statistical analysis, HIV positive and negative for variables were compared using the key square and [inaudible]. Survival analysis was preformed by Katheryn Meyer-Byers curves and compared by the [inaudible]. From the date of the [inaudible] diagnosis until death or sensory date with a maximum of 24 months follow up.

In the [inaudible] proportion of HAART [inaudible], HAART was [inaudible] as a time defendant variable. Variables

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with P values below 20 percent were selected for the multiple [inaudible] regression. The final [inaudible], retained variables with P value below 10 percent. Demographic and immunological data showed that age was significantly higher in the HIV negative group. Other variables like gender, alcohol abuse, drug use and monthly income were not. Clinical data showed significant difference between HIV positive and negative groups according to [inaudible] clinical forms, [inaudible] interruption due to adverse trends, rifampin use up to the end of therapy and [inaudible] of tuberculous therapy. These laboratory data showed that positive blood cultures was significantly more prevalent in the HIV positive group as well as resistance with [inaudible]. CD4 counts and viral load are shown for the HIV positive group, closer to TB diagnosis. HAART regimen use during tuberculous, this treatment I've presented in the slide and the more prevalent regimens included [inaudible].

In terms of follow up and end point, the lines of follow up were similar in both groups, but [inaudible] and tuberculous associated mortality were significantly higher in the HIV positive group. Although, surprisingly, the last follow up was higher in the HIV negative group. So, [inaudible] in the HIV negative group was significantly longer than in HIV positive.

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Survival in the HAART group becomes closer to HIV negative group than the group that did not receive HAART. However, compare only the HAART group with the HIV negative group and still remark a significant difference on survival.

[inaudible], time dependant, cost aggression analysis, the risk of death of the HAART group lost it's significance. It's remarkable the hazard ration of the HIV group without HAART. The risk of tuberculous there, according to the study variables, show that the [inaudible] tuberculous, Microbacterium and lack of rifampicin use were associated with the higher risk of death. The risk of death was also significantly higher among groups that presented resistance to rifampicin and [inaudible] adverse reaction. Although, most the drug resistance and the abandonment of therapy was not associated with a significant risk of death. All the variables associated with the risk of death were, HIV positive groups with CD4 counts below 200 in with an AIDS defining criteria based on another opportunistic disease.

The final model of [inaudible] regression analysis show that lack of HAART during tuberculosis therapy and [inaudible] to be associated with a significantly higher mortality.

In conclusion, despite the free assess on part in Brazil, tuberculosis mortality is a still significantly higher in the HIV positive group than in the HIV negative. Variables

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associated with the higher risk of death were disseminated to be resistance to rifampicin and lack of rifampicin in HAART during tuberculosis therapy. The analysis comparing HIV positive on HAART on HIV negative patients is still not conclusive.

We thank our patients that the agreed to participate in this study and to all health professionals involved. We also thank the Ministry of Science and Technology [inaudible] Brazil and [inaudible] for the financial support. Thank you very much for your attention. [Applause]

JOSE MIRO, M.D.: Questions?

MALE SPEAKER 1: I am Dr. [inaudible] from India. I have two questions. One is that you told that HAART was initiated after [inaudible] days of [inaudible] so, it was reversible, what was the rationale for using one month, was it CD4 dependent or something like that? So, you would start HAART [inaudible] after 30 days for all the patients and second, within your national program where there is the [inaudible] treatment to be followed, [inaudible].

VALERIA ROLLA, M.D.: For the first question, we initiated HAART after 30 days of therapy for [inaudible] patients because, our experience in the literature, we see that if we put the HAART the same time as TB therapy, adverse events are very frequent. So, we wait at least 30 days. This is how

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experience so that's why we do that, but it's just for [inaudible] patients. For [inaudible] treated patients, we just changed PI that is involved in HAART. The first question, I don't remember.

MALE SPEAKER 1: This is the first and second is also your national program.

VALERIA ROLLA, M.D.: Yes, we have [inaudible] in our program the first line is with rifampin but sometimes you cannot use rifampin so we have an option regimen without [inaudible] and that includes [inaudible] and ethambutol because our guidelines, in Brazil we use three drugs to treat TB, rifampin, isoniazid and pyrazinamide only. We have a very low incidence of low drug resistance in TB that's why, we use three drugs.

DAVID COHN: David Cohn from the United States, your baseline rate of MDR in HIV positives was a little bit surprising, do you have an explanation as to why where these prior patients previously treated, exposed in the hospital, any other explanation as to why that was the case in the [inaudible] study.

VALERIA ROLLA, M.D.: We are forming a new investigation about resistance in Brazil because the data we have is 10 years old, you know. So, we are looking to see what is happening now. This is [inaudible] results is also

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surprising for us because normally we believed that it was similar for both groups. Maybe it is because we [inaudible] so you know we are referral center so we see patients for all over Rio de Janeiro and not in the special site, so we have to look for what, these are the first results of our study, so maybe with more patients, we can see what happens next. Thank you.

MATT BOYD: Matt Boyd, Australia, two questions, one, what determines in your guidelines or at least in your institution which patients should receive antiretrovirals when being treated for TB and the second is, in this analysis [inaudible] does this [inaudible] TB or are some of these patients having recurring episodes and if so, how did you control for that in the analysis.

VALERIA ROLLA, M.D.: Yes, there are patients that were [inaudible] for the first TB in their lives, but there was also patients that had large parts of TB because in Brazil, TB is very huge and Rio de Janeiro is a city that has the hugest incidents of tuberculosis. So we have mixed, patient, [inaudible], patient for TB and [inaudible] patients. My memory is not very good so I don't remember the other questions you made, Can you repeat it?

MATT BOYD: Just the guidelines for initiating antiretroviral therapy in patients requiring [interposing] therapy.

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VALERIA ROLLA, M.D.: Yes. We have a guideline and we use HAART for patients with less than 350 CD4 counts and because we are an epidemic area, we are very, we have caution because sometimes, even with CD4 counts up to 350, we made a viral load to see what happened with this viral load and we make that 15 days after starting TB therapy, not to be bias and by the viral load of TB itself.

MALE SPEAKER 4: You had a few patients who are taking [inaudible] based regimen and also a few on [inaudible], the numbers are quite small, did you see any difference in the outcome of HIV treatment in these people?

VALERIA ROLLA, M.D.: Yes and another, and another, [inaudible] and in fact [inaudible] patients [inaudible] regimen works better because the side effects are less, but for experience in patients, [inaudible] doesn't normally work very well so [inaudible]. So we use both, but we prefer [inaudible]

JOSE MIRO, M.D.: Your question please.

MALE SPEAKER 5: Excuse [inaudible] from Sydney, Austria, I found it interesting that you showed that the patients that stopped the [inaudible] did worse, so have you gone any further to analysis this data because it was due to discontinuation due to [inaudible] after they started HAART or did you do intolerance, or what?

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VALERIA ROLLA, M.D.: Yes, lots of reasons for, first, is intolerance, it is very frequently in the HIV positive with low CD4 counts to have intolerance and sometimes we have to stop therapy and introduce drug to drug and sometimes we receive a test of sensibility and the resistance we have to change, that's why I said the people that use rifampicin all over the therapy and not for the first 30 days of 60 days, but [inaudible] is too small for HIV positive patients because our inclusion right here was to have a positive culture and we have lots of patients but I confirm a TB, it was like that. So, we believe [inaudible]

MALE SPEAKER 5: I have a question. Most of the mortality [interposing] in other studies when people start antiretroviral therapy with tuberculosis occurs very early on and the argument is generally made that maybe people have come in too late for treatment and might even be a reason to institute therapy earlier. You start at 30 days, but I'd bet interested to know what proportion of patients, when they die in relationship to antiretroviral therapy in TB. It looked like the [inaudible] curve looked like death continued over the entire course, so what proportion died in, let's say, the first 3 months.

VALERIA ROLLA, M.D.: In fact, most of death occurred at the first month, even the first 30 days, that why we made a

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time dependent to [inaudible] for therapy and in fact they arrive and die. Even if you give antiretroviral, maybe they die quicker because a lot of side effects and that's a decision to make that really is not very good because sometimes we want to put the therapy very early to prevent that and in fact, you have to interrupt all therapies and tuberculosis is our priority. We have to treat tuberculosis because the die to tuberculosis more than AIDS, so in Brazil, we have been working like that since the year 2000 and we believe that it works better that way. We don't know exactly what is the point, the best point to start on retroviral therapy, but we do like.

MALE SPEAKER 5: Right, well it does get to the issue which is a pertinent issue that everyone is interested in and that's what is the golden moment to start antiretroviral therapy in people with TB, so your patients, they die early on and the question I still think is open as to whether the starting point for antiretroviral therapy should be moved closer even in face of toxicity and other concerns, given that the mortality is early on and whether that should be some of the debate that comes out of this data actually is to either try to answer that question in Brazil or consideration of the earlier start in the therapy in very sick patients.

JOSE MIRO, M.D.: Is there any other question? Yes,
last question

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MALE SPEAKER 6: It's a general questions and [inaudible] but perhaps best addressed to the speaker but also to the panel, to what extent is [inaudible] preventive therapy or any preventative therapy being used in the national guidelines of each, particular in Brazil, but the other's on the panel might want to comment.

VALERIA ROLLA, M.D.: Yes, our guidelines [inaudible] all HIV positive patients effected by Microbacterium tuberculosis, so [inaudible] care when we see a patient HIV positive for the first time, we have to test them and to use isoniazid to prevent [inaudible], but you know it's [inaudible] infection in a epidemic area is a huge problem, but we are making a [inaudible] to see how long we can live with out TB using isoniazid at the beginning of HIV infection.

MALE SPEAKER 7: So in this cohort, did many of the people actually break through isoniazid and prevent new therapy or are most of them not taking isoniazid.

VALERIA ROLLA, M.D.: There's a new article that's been published by the [inaudible] that showed that HAART itself, it is able to reduce the risk of tuberculosis but if you give isoniazid, dose very much, as high as 7 percent, so you can prevent very, very much the incidence of [inaudible].

JOSE MIRO, M.D.: Okay, thank you very much

[Applause]

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We are on time on behalf of Dr. Friedland and myself,
we would like to thank all the speakers for their presentations
and all of you for your attendance of this meeting. Thank you
very much.

[END RECORDING]