

**2007 HIV/AIDS Implementers Meeting: Debates  
Use of Clinical Versus Immunologic Versus Virologic:  
Monitoring of Antiretroviral Treatment Response  
PEPFAR, The Global Fund to Fight AIDS, Tuberculosis  
And Malaria, UNAIDS, UNICEF, The World Bank, WHO, GNP+  
June 17, 2007**

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**MALE SPEAKER 1:** Without much ado, I have the pleasure to introduce to you Fabienne Shumbusho. Dr. Fabienne Shumbusho works with FHI Rwanda and she will be giving us our first presentation.

**FABIENNE SHUMBUSHO, M.D.:** Thank you. This presentation on importance of viral loads, before advancing to second line or salvage antiretroviral therapy regimens shows our observations in 75 Rwandan patients with clinical and/or immunological failure at the Yogho [misspelled?] Health Center which is one of the 25 health facilities supported by FHI Rwanda to provide high active on antiretroviral therapy. This health center is located in the Rwanda capital of Kigali.

As most of you know it, viral load is the best marker antiretroviral therapy efficacy and need to change for an alternative treatment. However, with limited access to these exams, WHO antiretroviral therapy guidelines the use of immunological and/or clinical response to guide when to switching to therapy failure should be done. This is what Rwanda has adopted in its guidelines, as there is limited capacity to do viral loads with only one laboratory country wide that offers this exam. According to the Rwanda National Guidelines, treatment failure criteria considered to suggest a

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change of antiretroviral therapy regimen on one or both of the following: first is clinical failure, and second is immunological failure. By clinical failure, we understand occurrence or resurgent's of opportunistic infections or other pathologies indicating clinical decline except in immunological reconstitution inflammatory syndrome. By immunological failure, we understand decline in CD4 to below pre-ART levels are more than 30-percent decrease from the highest CD4 level obtained doing treatment. In both conditions, to confirm treatment failure, adherence must be good.

In this presentation we want to share with you the findings, got at the global clinic, in order to see if clinical and/or immunological failure always dictates a need to change on to antiretroviral therapy. The medications use for 75 patients out of 728 started on first line ART and who were found with clinical and/or immunological failure, viral load was preformed systematically at the National Retro Laboratory, where quality of the exams is regularly controlled with PCR, in real time. Patients with detectable at low viral load virus, and this is less than 10,000 copies per milliliter. A repeated test was performed after three months in order to confirm the previous results. In the mean time, exposure to antiretroviral

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therapy measurement of viral load among these 75 patients was 20 ½ months.

What results did we get? As this graph shows, among the patients with immunological failure, four, which is 9.5-percent, had an associated virological failure, and in those with clinical failure, one, which is 4.5-percent, had detectable viral loads. In those with combined clinical and immunological failure, 1-percent had detectable viral loads. Overall, we say that only 8-percent, which is 6 out of 75 persons were found with virological failure. These patients with virological failure opposed the only eligible change for antiretroviral therapy regimen. The remaining 92-percent, this is 69, had undetectable viral load and did not need to change treatment. They remained on their regimen.

On this table, the six patients found with detectable viral load are in the last two columns. Among them, two have low increases. This is the second column. Less than 10,000 copies per milliliter, and four had significant increases. For these two patients, repeated exams after three months were performed in order to document the presence of detectable viral loads.

Results showed a persistent detectable viral load in only one of the two patients, and the other one joined the

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group of undetectable viral loads. In total, only five patients had the criteria for a second line antiretroviral therapy regimen. Overall, what these doctors show is that there is another detection of cases that needs regimen change according to WHO criteria of treatment failure.

And now, let's look at the total patients on non-retroviral therapy at the Global Clinic. The findings we had show that among 728 patients on antiretroviral therapy, only 1-percent, which is 5 out of 728, among those who met WHO treatment failure criteria, had a real need of treatment change according to viral load results performed. On the other hand, if you consider the literature, data and finding, it is expected that after 1 or 2 years of therapy, between 7 to 12-percent of patients on antiretroviral therapy will have detectable viral loads.

If we assume that this can be applied to patients at [inaudible], we can expect that approximately 47 patients would have been detected with viral load failure if the exam was offered routinely. These were there from missed cases due to the absence of indications of viral load testing.

In summary, let's not the principal implications of changing or not changing antiretroviral therapy regimen in the absence of viral load testing with WHO guidelines that we use.

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First, if we consider all patients with clinical and all immunological failure as an indications for antiretroviral therapy regimen change, without eliminating those undetectable viral loads, we often detect cases to put on second-line antiretroviral therapy. Secondly, if we ignore patients with clinical and/or immunological success and do not assess their needs for antiretroviral therapy regimen change, we under detect cases by missing all those who would be detected with viral load exam.

Before finishing, two main recommendations are formulated from the findings presented here. First, review and notify national guidelines to include viral load testing indications with consideration of existing and potential capacity to do it. Secondly, conduct an assessment of biological outcome of first line ART at large scale in Rwanda in order to give emphasis to our findings.

Finally, I end this presentation with a reminder, let's not forget the good adherence to first line antiretroviral therapy, but uses need to advance to second line. Thank you.

[Applause]

**MALE SPEAKER 1:** Thank you, very much indeed, for that presentation. I am sure there are some people with questions but we'll go on to listen to the first three speakers. The

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next on is Johan Van Griensven, he works with MSF and he's going to give us the second presentation.

**JOHAN VAN GRIENSVEN, M.D., PH.D.:** Thank you. Next please. So, as we all know the WHO guidelines for every treatment of last year, they encourage access through viral load measurements but they also state that within the public health approach, through ART programs, it's difficult to apply. So, the providers with several immunological criteria to use for therapy, therapeutic decisions. The major ones, you've seen in the present also of Dr. Fabienne or the first case dropped below baseline CD4 values, and the second one is a 50-percent or more from fall from peak values. Next.

The problem is that there are few data that validates this progressed criteria, so the question we have here for the program in Rwanda, is to assess the performance of the WHO proposed immunological criteria in Rwanda. So, the question was, to what extent does immunological failure predict virological failure. The data I'll show you comes from the ARV program and it's supporting two health centers. The program was started at the end of 2003, there are a bit more than 2,500 patients on ARV and seems it quite an old cohort, as part of the routine evaluation of long-term problems, viral load was performed routinely after one year.

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So we had viral load results of a bit more than 860 adult patients, so viral loads taken after one year on ARV and we used these data to calculate both criteria, as proposed by WHO, so the first one is to compare the recent values, at the time the viral load was taken, to the baseline value, is the first criteria. The second criteria is to compare the recent value to the peak value on treatments. So we calculate sensitivity, specificity, and predicability to quantify the performance of these criteria. If you look at the data, at least the data that we have in our cohorts, for the [inaudible] criteria, and let's focus first on sensitivity. We receive for the first criteria, which defines immunological failure as a drop below baseline values of baseline CD4 counts, we get a sensitivity of 12.3-percent. If we look at the second criteria which compares the recent values to the peak values, which defines failure as a drop of more than 50-percent, we come to 23-percent. If you combine them together, this gives overall performance of sensitivity of 27-percent. To visualize, it may be a bit more clearly, we can look at these data in a two-by-two table, where we actually compare our CD4 count tests, so the immunological criteria, with the gold [misspelled?] standard, the viral load measurements. Virological failure was defined as the viral load more than 40 copies per ml, so you

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can see in the first column, that we have about 12-percent of patients in the cohort reassessed, that had virological failure, so 88-percent have undetectable viral loads. If we stay in these columns, we can calculate the sensitivity, which, for sensitivity, we actually want to see all the patients with a detectible viral load, how much did we pick up with our CD4 count tests? Then we only come to a bit more than 25-percent, actually 27. Same, we can do for specificity, where we come to 82-percent. Another way of looking is starting from the CD4 count tests, and then evaluating what is the use, what does it tell us, concerning the viral load measurements. So, these are the predictive values.

If we look at the older patients where their immunological failure, based on the criteria we use, we have a positive predictive value of 17-percent. So of the 100 patients we have a positive test on our immunological criteria, only 17 have detectable viral load. The same can do for the negative predictive value.

Overall, this test, there is some value, but let's say the performance is quite poor. The main problem is the false positives and the false negatives. We have there, for the false positives, we have 16-percent, so these patients with an undetectable viral loads who we would define as having

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treatment failure based on the CD4 cell counts. These patients, if it would be strict, like was also addressed in the other presentation, we would put on second-line therapy without any needs.

The other problem is false negatives. So, these patients that have detectable viral loads, we don't pick them up with a CD4 cell count measurements.

If you want to prove on these tests, we have a few options. The first is to work on the first column, and this is how do we define immunological failure? The second option we have is what do we define as virological failure? How strict are we? The third option is, to look at the population where we will assess for immunological or virological failure.

If we take the first option, we try to modify it by the CD4 count thresholds. Next. For example, we can say that maybe the drop in 50-percent, it's maybe not strict enough. Maybe we should define failure, or we could define failure, as a drop of 30-percent from peak values. Then, indeed, we have a sensitivity which goes up to 38-percent. Of course, we lose some specificity. Another proposal we can make is maybe the drop below baseline values, maybe we should, we could propose that if a patient doesn't increase from baseline values with more than 50, we can define as a treatment failure. If we do

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this, we come to 33-percent of sensitivity and if you combine this criteria, we have a sensitivity of 56-percent, but we lose at specificity. Next.

Another way of looking at different thresholds, I'll have to be short, this, to plot our C-curves, who summarize the performance of the tests at all different thresholds. In general, you want the area under the curve of at least 0.7, an area on the curve of 0.5 is a completely useless test. For the two criteria, the first criteria is comparing current CD4 count to baseline, we have an area on the curve of 0.53, which is quite low. The second criteria gives the area on the curve of 0.62, which is a bit better, but I think it might also have to do with the fact that we do do an assessment quite late, so quite low on therapy. Next.

Maybe up to now, we can say that even if we play a little bit with the CD4 count thresholds, we win a bit at some point, but we lose at other points.

The second question we can ask is, how do we define virological failure? Maybe CD4 viral load at 40, maybe it's too strict. Maybe we can use a threshold of more than 1,000 at treatment failure, at this will eliminate virological blips, and especially it's important if you only have single measurements.

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Another argument proposal you can make is, maybe we have to look at viral loads that's more than 10,000. Since its new guidelines, they define importance or high viral loads as more than 10,000, at least, is where they propose to changing to second line therapy.

So if we look at the performance of our tests of different viral loads thresholds, let's just focus on the green line, this is the line which summarizes both criteria together. So you see, with a viral load of 40, we see that before the performance is quite poor. Next.

If we define failure of more than 1,000, it improves a bit, but only slightly. Next.

If we go to a viral load of more than 10,000, as a definition of treatment failure, the improvement is more pronounced, we come up to an error on the curve of almost 0.7, so these data suggest that the potential of CD4 counts will detect viral loads more than 40, might be limited, if we're happy with the detection of viral loads more than 10,000, the potential is a bit high. To put a number on these, to quantify these differences, if we look at the viral load less than 40 WHO criteria we have a sensitivity of 20.27-percent. If we define or we have a viral load of more than 10,000, we come to a sensitivity of 47.6-percent. For more defined criteria, we

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start at a sensitivity of 56-percent, which adds up to 81-percent, if we define virological failure as a viral load more than 10,000.

To put all these data together, there is the performance overall is quite poor, but if we're positive, I think we can still look for some good use for CD4 counts, and one is to use it or to consider it as a screening tool. To select the patient where we need to do a viral load. If we would use WHO criteria that way we would do viral load measurements in 20-percent of the patients and we would detect half the patients which need second line therapy. If we modify the criteria a bit, we do viral loads in 57-percent of the patients and we would detect 86-percent of the patients who need second line therapy.

Last question is to what extent the population affects our results. There's a lot to say, I'll just focus on one point. What affects do baseline CD4 counts affect our results. Next

There, we see what is often seen by other people, on the left side you see the performance with a baseline CD4 count of more than hundreds. If you compare this with the other plots on the lines below, we see that the area on the curve is

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definitely higher for lower baseline CD4 counts, so the performance is definitely better. Next.

So to put all these data into a few conclusions, I think we can say that overall, the performance of the WHO immunological criteria is poor in predicting virological failure. We have some improvements to some extent if we play with different thresholds for immunological failure, viral load thresholds sub-groups, good enough probably, to use it as a screening tool. Next.

Strategies to explore, between proof and this criteria, will defiantly have to be addressed. Maybe we have to consider the option of repeat measurements, maybe more important to incorporate clinical data, laboratory data, to increase the pretest probability, and these are data just from one program. I think it's very important to consider other programs, and there are other interesting reports already published.

At the end, I think these data show that we need to go at the, in the long term to increase access to viral load measurements, which is adapted to resource or resource constraint settings, which is incorporated into a comprehensive approach, works closely with counseling and programs and we need to go for development of alternative tests, at a reduce prize, with that of logistics, no need to refrigeration,

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ideally can be done on site, result available the same day, and minimal training required. The same way we do a pregnancy test, HIV test or the glucose measurements. Maybe also have to consider that we don't need exact values, at least for these settings, but maybe different thresholds can be useful. Next.

There are already a few interesting initiatives on the way. One of them is based in Cambridge University which [inaudible] is trying to support, where they're trying to make a very simple test, a kind of a dipstick which gives the results the same day, very fast and give you different thresholds. The thresholds of 10,000 could be used to define which patients need second line therapy. Detectible viral loads could be defined to direct patients for intensive counseling, and another option is that it could be used for diagnoses of HIV in young children. Next.

Finally, I would like to thank all these services for the support we've got and I'd like to thank you for your attention. Thanks

[Applause]

**MALE SPEAKER 1:** Thank you Johan. I think the presentations are getting quite interesting. We'll hear Grace, Dr. Grace Magembe from MDH Tanzanere, then afterwards we'll

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take some questions on these three presentations and then go to the second part of this session.

**GRACE MAGEMBE, M.D.:** Thank you. Good afternoon. Just a small clarification, I'm Grace Magembe not Majembe, sorry for that. In a few minutes come, I'm going to discuss with you our experience in the use of immunological bases of virological criteria for defining treatment failure. This is an experience from a program known as MDH. MDH is a corroborated program between [inaudible] Investive College of Health Sciences, the [inaudible] City council and [inaudible] School of Public Health. This is a program which is providing care and treatment for people living with HIV/AIDS and it's based in [inaudible].

The outline, I'll have an introduction, background, objectives, mythology, results and then we'll have a discussion, conclusion and, as you can see.

Virological failure [inaudible] followed by immunological, and then clinical failure. However, these events may be separated by months to years. Patients with immunological and clinical failure, despite they might present with immunological and clinical failure despite having suppressed [inaudible] and these do not warrant change to second line therapy. Next.

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The World Health Organization has located CD4 cell count to identify treatment failures in resource limited countries. However, monetary plasma HIV1 arraniate [misspelled?] labels, that is viral load. It's a valuable tool to identify virological treatment in patients taking antiretroviral drug therapy. There has been several virological reports, in the developing world, who have recently reported they did not use these tests due to resource constraints. Next.

So, Tanzania being one of the countries which is resource constrained, most of our care and treatment centers do not have access to viral load [inaudible], so ART regimen changes are usually based on immunological and clinical criteria. How do we define that? Immunological failure is defined as a 50-percent drop in CD4 count from peak value or [inaudible] ART baseline or lower and clinical failure is defined as a progression of disease, with the development of opportunistic infections or malignant, appearing three months after installation of antiretroviral therapy. If viral load tests are available, the definition of virological failure is, we have two definitions, we have primary virological failure, and secondary. Primarily virological failure is less than 10-fold drop in viral load after 6 to 8 weeks of therapy, and

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secondary virological failure is a 10-fold increase from lowest recorded level. However, virological points require a baseline and a full [inaudible] viral load. Next.

So, at [inaudible], MDH, MDH clinics, viral load tests are available. However, through a recently introduced, initial we never used to have viral load tests. In our clinics, the cutoff point for virological failure is defined as the detect of a viral load that is more than 400 copies per ml, after being on treatment for more or 24 weeks. That is six months. Our extending encouraging procedures in defining treatment failure, first of all we have what we call expected immunological failure, this is a CD4 drop of more than 50-percent, as I said before, and for those people who will qualify in this, they'll end up going through what we call an comprehend [misspelled?] complete CD4 count. Okay, within one week, and then, after that we do a viral load test and then those who have detectible viral load are the ones who will be switched to second line therapy.

Objectives. The first objective is to assess the role of CD4 testing defining immunological failure, and to analysis the use for [inaudible] viral load results in enhancing accurate and defining failure.

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My thoughts, this report is based on 96 of 1,657 patients on ART who had some suspected immunological failure and the fall-off period for these patients was between November, 2004 and November, 2006. Inclusion criteria where the age of 18, more than 18 years, HIV positive treatment [inaudible] patients, and the patients had received ART for the period of 8 to 12 months, and they were suspected to have immunological failure based on the 50-percent drop, and they had a viral load CD4 count, a viral load repeat CD4 count, and a valuable viral load test results. The CD4 cell counts were used by measuring by using [inaudible] and a baseline of 4 months and 8 months, 8 months and 12 months up to [inaudible] of treatment and viral load tests were done by co-sample, this is rushed at [inaudible], only once to confirm those who are true failures. Next.

Out of the 1,657 patients with suspected immunological failure, that is from a single CD4 result, only 994, which is 60-percent of the patients were confirmed. Among those who were confirmed as having immunological failure, that is with a repeat CD4 count, only 179 patients, which is 18-percent, had detectible viral loads. Similarly, of the 663, which is 40-percent, of those who were not immunological confirmed, 46 out of them, which is 7-percent, were found to have a detectible

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viral load, while the 617, which is 93-percent, had undetectable viral loads. This analysis shows that the use immunological criteria, alone, cannot precisely predict patients with virological failure, and may lead to significant misclassification of therapeutic response. Similar results have been obtained in other studies. Compared to a single CD4 result, or a single CD4 test, a complimentary CD4 count reduces the number of patients labeled as immunological failure, who had otherwise be put in a second line regimen, by 40-percent. Even with the repeat CD4 count, about 82-percent with confirmed immune failure would likely have been switched to a second-line ARV therapy prematurely if viral load results were unknown.

Seven-percent of patients who were not confirmed to have immunological failure by repeat CD4 tests had detectible viral load which means, by using this criteria, they'd have been kept on a failing regimen. Next.

Viral load access enhances accuracy of defining therapy first-line failure for a substantial portion of patients with immunological failure, and spared more costly regimens for future use.

In conclusion, immunological monitoring in result limited settings has value, but it does not precisely predict immunological failure. So, use of viral load testing may

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reduce the public health risk of patients remaining on a failing regimen and save them the additional cost of second-line therapy that can be preserved for future uses when ARV therapy is more accurately identified.

Limitations of, as I said before, we didn't have a baseline viral-load results for our patients, and this was not a controlled study, it was based on the available data. Next.

I'd like to acknowledge those people there and, thank you very much.

[Applause]

**MALE SPEAKER 1:** Thank you Dr. Magembe. I got your name correct this time. I think, these three presentations need to be addressed together, and there are two microphones, we have maximum of about 5 minutes, will that be enough for questions? Five minutes, for those who have questions at this stage. Please go to the nearest microphones. Please keep your comments and questions brief.

Let's start the nearest here.

**CHRISTA FAMON:** Thank you very much, my name is Christa Famon [misspelled?], [inaudible], thank you very much for the presentations. The main issue I want to raise is I do not really understand, because the data is not correlated to any kind of long-term outcome, whether we just play with

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sensitivities and specificities, and we really do not understand what those markers mean, even for transmission probability. If I have, on the ART, an increase of viral load, I cannot simply make the conclusion that there's a risk of for, the epidemic in terms of transmission of resistant strain to the larger population, because I do not know anything about those viruses and that transmission probability. And that is not just viruses. Thank you.

**JOHN KAPLAN:** I'm John Kaplan from Atlanta in the US. A comment and then a question for the panel. I think we're all impressed. There were three very excellent presentations of unique settings, and these very excellent settings in which our colleagues here are working, at predicting a value for immunological or clinical failure, however it's defined, for virological failure, the positive predictive value is quite poor. A lot of other programs around the world, the work which is not quite, perhaps, as excellent as these, or the level of viral suppression is not so great, the predictive value would probably be somewhat better. However, that's just the point. The question is, of the types of discordant that we usually think about, virologic and immunologic discordant, I'm impressed that there's an awful lot of the type of discordant were we have clinical or immunological failure despite viral

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load suppression in the African context. Why is that? Is there some battering of the immune system that's going on in the African context, I wonder if anyone would speculate?

**MALE SPEAKER 1:** Moses [misspelled?], do you want to make a comment?

**MALE SPEAKER 2:** Well, I just want to ask, is it a question or a comment? Of course, we all know that both CD4 counts on viral load are important, because both have been independently associated with mortality, so maybe, both are important in their own right. But, on the other hand, we know if the viral load is present, if it's detectable, then the drugs are not doing what they're supposed to do. I mean, they are supposed to make the virus undetectable in blood. I just want to ask some question to, I mean, some thoughts about the people in the room. Right now most of our programs, we are not doing viral load and clearly these three presentations show how the WHO criteria for treatment failure is just, not good enough. The sensitivities are very low and then you've got a lot of discordance where the immunologic and virologic discordance [inaudible], so it's just, we are reading the duck when we don't do viral load. I'm not saying we should not do CD4 counts because they also matter, I just wonder whether some people think doing a viral load once a year, I mean, what is

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the cost of not doing it? What's the cost of switching versus not switching, or would it be more cost effective if we did a viral load once in a while? It seems this is an implement as meeting, I would be happy to hear some practical suggestions about [inaudible], or maybe we shall wait for Jono's talk which is-

**MALE SPEAKER 1:** Okay, now, the three presenters, just quick comments and we'll move on. We'll have some time today, at the end, to come back to some of the questions that might overlap with other presenters.

**FEMALE SPEAKER 1:** I don't think I really have an answer to the second question. Discordance, why is it that we have discordance between clinical and ongoing immunological response and virological response? I don't have an answer. We didn't, our team didn't have an answer. I don't [inaudible]-

**FEMALE SPEAKER 2:** I think we have the same experience, we also don't have an answer. Maybe we need further studies to evaluate these, but even in our country we still have not an answer on this, but we are seeing that people have well suppressed of [inaudible] despite having immunological failure and clinical failure.

**JOHAN VAN GRIENSVEN, M.D., PH.D.:** Concerning the discordance responses, we might have to look into details, but

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there is some interesting data from the ART Inc. Group, it was published this year, where they describe in more than 1,000 patients discordance responses, moved in national cohort, and I had in mind they had like quite similar results as the ones that you've seen in Europe, the States, so I had more in mind for discordance responses are a general problem. We have it in Africa, we have it in Europe, the States, and I don't think the extent of the difference is very pronounced. It's, [inaudible].

**MALE SPEAKER 1:** I think some of the answers might come in some of the next presentations. You wanted to make one, let's have your last comment.

**DR. MAR MARCHOS:** I am Dr. Mar Marchos [misspelled?] I am the director of medical services in one of the [inaudible]. My comment is directed to a previous speaker, talking about immunological failure based on the CD4 count, to me, I think, it's very [inaudible] to conclude when you deal with CD4 count. I know, of course, there are many factors which produce CD4 count. If you can vary the viral load, I realize this will help you to know that your drugs, you combination is working. Viral load goes up and the patient is taking your drugs correctly, [inaudible], therefore, you conclude that this combination is useless. Then we have to know, which drug can

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repress this, now to do, this is the question. Do you then do it when you're wasting your time? Does it come a problem, so giving these drugs like we eat beans, or [inaudible] is a waste of time. We have a trial facilities to know which is which. I have had many people commenting, talking about [inaudible], toxicities, [inaudible] when you combat that you commend the [inaudible], when you know that he is really innocent. So I think we see how programs in the managing patients. I'm insisting on basing your management on a CD4, as we know that CD4 will increase faster in young people, the other people it may take time, [inaudible] slowly. So the message you've given to me is viral load. Thank you.

**MALE SPEAKER 1:** Thank you Dr. Marchos [misspelled?] for that comment. [Applause]. Thank you.

I think now we'll move to the second part of our afternoon session. I have the pleasure of inviting Jono, Dr. Jono Mermin, CDC Kenya. We like to say CDC Uganda-Kenya has been in Uganda recently and spent quite a lot of time there. Jono, you're most welcome.

**JONO MERMIN, M.D.:** Thank you. Good afternoon, I'm please to present, today, some preliminary results from a study examining the efficacy of laboratory monitoring of adults taking antiretroviral therapy in Uganda.

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For the first part, I'll discuss morbidity and mortality across the three arms of the study and for the second part, Professor Jim Kahn will present cost effectiveness results. I'd like to mention up front, that this study is the result of years of work, by many talented people, and even more than I could list in acknowledgment slide at the end of this presentation.

In thinking of HIV care and treatment in African and elsewhere, in addition to limited services at most health center, several issues need to be addressed. Including the fact that there's a dispersed population with limited access to transportation. For example, in a recent program in Malawi, access to patients to ART was associated with the cost of transport to the health center. If transport was more than \$1.00, then patients were four times less likely to receive treatment. At the same time, prices for ART drugs have decreased dramatically in Africa over the past few years, and this has allowed an increase number of people to take ART. However, the laboratory facilities capable of providing viral load and CD4 cell count testing are often limited, and routine testing is expensive, the annual cost of which can exceed a year of first-line ART drugs. This has resulted in many people in Africa not receiving any, or in treatment laboratory

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monitoring. WHO guidelines for ART in, research limited settings, as the other speakers have mentioned, support the use of CD4 cell count measurements alone, but the efficacy of this practice, with regard to clinical outcomes, has not been evaluated.

Many studies have documented that baseline, CD4 cell count, and viral load, are associated with prognosis, and CD4 cell count is useful in determining clinical eligibility for ART. In addition, having high viral load during ART, is associated with worse clinical outcome. Because of this, routine CD4 cell counts and viral load are recommended every 3 to 4 months in the US and Europe, with the expectation that frequent measurements will detect treatment failure due to resistant virus and allow rapid change to another ART regimen.

In 2003, with PEPAR support, we established the Home Based AIDS Care Program. HBAC adds ART and TB care to a care and prevention package for 1,000 people with HIV. Family VCT, sexual behavior, and drug adherence counseling, is provided to participants. ART is provided to all eligible adults and children in the household, and weekly home visits are conducted by lay workers who deliver medications and use a standard symptom questionnaire. No scheduled clinic visits are made after enrollment. Next slide.

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HBAC contains a three-armed, randomized trial evaluating different drug efficacy monitoring regimens. We wanted to see if there were any difference between monitoring using quarterly viral loads and CD4 cell counts, arm A, versus quarterly CD4 cell counts, arm B, versus home visits alone, on arm C. The main outcome were severe morbidity, essentially new AIDS defining events, and mortality, after three years of follow up, and the cost effectiveness of the different regimens. The study is situated in Tororo and Busia districts of Eastern Uganda on the border with Kenya. Eligibility criteria included having a CD4 cell out less than 250, or WHO Stage 3 or 4 disease, and AST or ALT less than five times normal, a cretonne [misspelled?] clearance greater than 25, and a Kornoski [misspelled?] score greater than 40-percent.

Our first line regimen consisted of Nevirapine, Lamivudine, Stavudine with afrabrine<sup>s</sup> for combatant TB treatment and our second-line regimen included Lopinavir/Ritonavir, Didanosine and tonopavir [misspelled?].

Blood for viral load and CD4 cell count measurements is reflected quarterly from all participants in their homes. Data were collected from clinical visits and hospitalizations, and a clinical case conference including a multidisciplinary team of physicians, nurses, pharmacists, and counselors, discussed and

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recorded information regarding all deaths, hospitalizations, opportunistic illnesses, abnormal labs, and approved any changes in ART regimens.

In all arms, the first response to the indication of treatment failure was adherence counseling and support. For arm A, the definition for neurological failure was flexible, primarily focusing on having two consecutive detectable viral loads after six months of therapy. However, if viral loads were 50 to 5,000 copies, and the participant was clinically well, we could continue with a first-line therapy. Other definitions related to CD4 cell counts and clinical events could also be used, but a hierarchy indicated a priority for viral load in our [inaudible]. In other words, if viral loads was suppressed, we did not change regimens in the face of morbid events.

For analyses presented today, we used a definition of failure as two consecutive viral loads of greater than 500 copies. For arm B, failure consisted of persistently defining CD4 cell count, measured on two separate occasions for clinical failure. For arm C, definitions for clinical failure included, unintentional weight loss of greater than 10-percent, appearance of a CDC category C illness, diarrhea or fever greater than one month without correctable cause, or newer

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recurrent oral esophageal or vaginal candidiasis without a known cause.

We used Kaplan-Meyer techniques for initial analysis of time to first event of severe morbidity for mortality and to death alone. We used Cox proportional hazard models to adjust for variables at baseline, while comparing outcomes across arms. We also used per-person aggression analysis to examine rate of hospitalizations and severe morbidity. We used both intention to treat approach, from date of randomization, and a protocol approach, starting greater than 90 days after initiating ART, because the first laboratory results, after baseline, were not drawn until three months after initiation of therapy.

1,116 ART naive individuals were randomized and 1,094 started ART. 8-percent had Stage 4, and 31-percent had Stage 3 disease. The median follow up was three years. There were 126 deaths or 11-percent of the population. 47-percent of which occurred in the first three months of therapy. There were 148 new AIDS defining illnesses, 57-percent of which were in the first few months. 61, or 5.8-percent of participants had two consecutive viral loads greater than 500, after the first six months. 28, or 2.7-percent of participants, switched to second-line drugs.

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This table presents participant characteristics of baseline. Participants generally had advanced disease with a median CD4 cell count of 130 and a median viral load of over 200,000. The only difference among arms is that arm C, the clinical monitoring arm, had fewer women. Next slide.

This slide shows Kaplan-Meier curves for time to an event for severe morbidity or mortality. On the left, the data is presented from intention to treat prospective, and on the right from a protocol analysis. For both, arm C, the clinical monitoring arms, shown in red, had a significantly higher rate of morbid or mortal events than arm A, the viral load arm, shown in black, and the CD4 cell count arm in blue. In the protocol analysis, this difference was also significant for comparison between arm C and arm B.

These graphs present Kaplan-Meier survival curves. There was no significant difference among the arms in survival using the intention to treat for protocol analysis. However, because there were differences in sex distribution at baseline, and because sex and other factors have been associated with clinical outcomes, we developed Cox proportionate hazard models and we were able to adjust for these variables. Next slide.

In an intention to treat analysis, adjusting for age, sex, and baseline CD4 cell count, viral load, body mass index,

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and CESD depression score, the rate to first severe morbidity or mortality events was 1.5 times higher in arms C than either arms A or B, shown in the lavender ovals. There is no significant difference between arms A and B, shown in the light blue oval. We found similar results in a pro-protocol analysis with the rate of events about twice as high in arm C than either arms A or B, there was again, no significant difference between arms A and B.

When we examine rates of specific disease morbidity, there was a higher incidence among arms C, the clinical monitoring alone arm, than arms A or B for Tuberculosis, PCP, cryptococcal disease and Kaposi's sarcoma. There was no difference in the rate of these diseases between arms A and B. For both the intention to treat and for protocol, Cox analyses rates of mortality, there was a non-significant trend between arm C and arms A and B. There was no difference between arms A and B in mortality rate.

To examine potential reasons for this difference and outcomes for arm C, we look more carefully at treatment failure. There was a similar number of people with virologic failure after the first six months of treatment. Sixteen in arm A, 26 in arm B, and 19 in arm C. During follow up, having viral loads greater than 500 was associated with increase

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proportion of people with episodes of severe morbidity or mortality, 18-percent versus 10-percent.

This table present information regarding response to treatment in the different arms of the study. Please note, that 90-percent of patients had complete viral suppression at one year. In other words, less than 50 copies/ml. This is the highest suppression rate reported in the literature and attests to the excellent level of adherence achieved by the participants, probably because of weekly delivery of medication and a strong problematic effort towards adherence counseling. The left most column presents the failure rates described earlier. The second column shows that only a proportion of these participants with virologic failure would change to second-line therapy. About half in arm A, and less than 1/5 in arms B and C. Please also note, that in the last column, those changed to second line therapy, all in arm A and B had treatment failure defined by viral load, but only 12-percent of arm C had detectible virus. Next.

What happened? First, please note the first row of this table that presents the last median viral load of those patients with detectible virus before changed to second-line therapy. There's a non-significant trend toward a higher copy number in those arms without viral load monitoring. Once

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changed to second-line therapy, at six months, all participants, regardless of arm, did quite well, with all having either an undetectable viral load, or one below 500 copies. However, when we examine the number of days with detectible virus before drug change, it was considerably higher in arm C, 548 days compared to less than 200 days in arms A and B. It appears that arm C patients had a longer period of time with detectable virus. However, you are also probably interested in determining what happened to the people who had detectable virus but did not change therapy. In the second-to-last row, please see the median value for the second viral load, greater than 500 copies/ml for people who did not change therapy, and in the last row, see that six months later, arm A participants had undetectable levels, arm B had 1,340 copies, and arm C had 7,340. Although we have not yet analyzed the adherence data, in arms A and B, participants with either viral load or CD4 cell count measurements that indicated failure, were counseled and improved medication adherence and this may be the reasons their viral loads improved without the need for a change to a second-line regimen. However, in arm C, we did not detect drug failure and people continued to have elevated viral loads. Of note, of the 17 people with detectible viral loads in arm C, they were not changed to second line-therapy,

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there were two deaths and no episodes of new AIDS defining illnesses. Next slide please.

This slide presents data on the opposite question. What happened to the 15 people in arm C, changed to second-line therapy with undetectable viral loads? All were changed because of new AIDS defining events, indicating clinical failure. These included six cases of cryptococcal disease, six of TB, four of Kaposi's sarcoma, two of cervical cancer, one of CMV and one of a recurrent pneumonia. All occurred greater than one year after starting ART.

These data raise the question, why did arms A and B do better than arm C? It was not only that there was an earlier regimen change in failing patients, because less than 50-percent of participants in arm A and B had viral loads greater than 500 were changed. Data that viral load became undetectably low in people in arms A and B that did not change therapy suggests that adherence interventions resulted in subsequent viral suppression. In these arms, viral load and CD4 cell count monitoring probably detected the adherence issues before the occurrence of morbidity or mortality. Clinical criteria, alone, were poorly sensitive in detecting clinical failure and poorly specific in restricting drug changes to those participants with an elevated viral load.

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However, even in arm C, the people with detectible viral load, whose regimens were not changed, did relatively well.

In conclusion, all study arms performed well with one year mortality in arm C of 9-percent, lower in all but one study in Africa and rates of viral suppression were high. Lay workers can effectively deliver drugs, support adherence and monitor patients without scheduled clinic visits, and supporting adherence is an important determinate in success.

Do these data provide any guidance to answer the question of how should ART be monitored? Clinical monitoring alone was associated with an increased rate of new AIDS defining events, and a trend towards increased mortality. This supports efforts to build laboratory capacity and provide laboratory monitoring. There was no benefit seen for adding quarterly viral load measurements to CD4 cell counts, supporting WHO guidelines, and suggesting that priority should be given to expanding access to CD4 cell count measurements, at least in patients adhering well to ART.

As people presented today, CD4 cell counts do not accurately predict viral load failure however. In this study, following resulted in equivalent clinical outcomes.

Lastly, it would be important to determine cost effectiveness and long-term outcomes for follow ups greater

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than three years, in case over time, routine viral load measurements might become beneficial as an increasing number of people develop resistant virus.

Thanks. I just wanted to thank the people listed here and all-

**JIM KAHN, M.D.:** -clinical monitoring, that is arm B versus arm C, and also, separately, adding viral load to clinical and CD4 monitoring, that is arm A versus arm B. To do this, we calculated what's called an incremental cost-effectiveness ratio, or ICER. This is the difference in cost for two options, two monitoring options, divided by the difference in health outcomes for these two options. Thus, we compare each option to its next less expensive alternative in order to assess the cost and health value of each incremental infusion of resources for ART monitoring. Next slide please.

We measure health outcomes using disability adjusted life years, or DALY's. DALYs averted. DALYs are by definition a negative health outcome, so you avert DALYs with reduced mortality and reduce morbidity. We use DALYs because it puts, this measure puts mortality and very morbidity outcomes onto one single metric. Next slide please.

Our model uses health inputs from the clinical trial using the intention-to-treat analysis, even if the differences

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were small or non-significant. Our time horizon is the three years of the trial plus future DALYs and costs due to the reduced mortality rate which occurred during the trial. A cost input comes from the HBAC program and other sources. We looked at incremental costs, health benefits, and cost effectiveness-ratios across the arms. We did an analyses for the base case, that is our best estimate of values and sensitivity analyses in excel. Next slide please.

Here is one key input. The CD4 count test, the test kit, we use a value of \$3.80. The cost per test, including personnel and other inputs, is \$4.68 or about \$19.00 per year. The viral load kit is \$27.00 and the total cost for the viral load test is \$29.64 or about \$119.00 per year. Next slide.

Another key input is the serious morbidity and associated DALYs. We listed the serious morbid events that occurred and we attached a value for DALYs to each one based on expert opinion of the clinicians working in Tororo. We then sum these for 14 severe morbid disease, got the total episodes by arm, the total DALYs per hundred person years and the crude estimate, and then further adjusted that for the observed multi-vary of hazard rations. Next slide please.

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The annual cost of ARV's for a first line regimen was estimated at \$182.00 per person-year of therapy and for second line, \$1,080.00 per person-year of therapy. Next slide please.

Here are our first results. These are the cost and health results by arm. For arm C on the right, the estimated total cost, per hundred-person years is \$55,000.00; for arm B, \$66,000.00; and for arm A, with all three types of monitoring, \$81,000.00. For health outcomes, the worst outcomes, that is the most DALYs, occurred in arm C, 45 DALYs. Note that almost all of the DALYs were due to mortality, 44 out of 45. For arm B, we estimated 32 ½ DALYs, at which, again, almost all were due to mortality; in arm A, 28 DALYs, which almost all were due to mortality. Next slide please.

This is our second set of results. The incremental cost and health comes and cost effectiveness ratio. We compared arm A to arm B, and arm B to arm C. Arm A, the total cost was \$15,000.00 more than the cost for arm B. The difference in DALYs was about 4. The cost per DALY inverted, or the incremental cost effectiveness ratio, was \$3,600.00. For comparison of arm B to arm C, that is CD4 monitoring versus clinical alone, the difference in cost was \$10,700.00, the difference in DALYs about 13 and the cost per averted DALY, \$831.00. Next slide please.

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We did a sensitivity analysis on the price of test kits. The value of one represents our base case numbers. The pink line with triangles shows how the cost of the viral load test kit affects the cost per DALY averted in the comparison of arm A versus arm B. If the price drops to 1/3 of the base case value, then the cost per DALY averted is about \$1,900.00 and if it's three times as high, it reaches up to about \$9,000.00.

The blue line with open circles shows the same analysis for the CD4 test kit cost and the comparison between arms B and C. At 1/3 the cost of the starting value, the dollar per DALY averted, drops to about \$800.00, and at the other extreme of a three times higher cost for the test kit, it reaches about \$1,200.00. Next slide please.

We also looked at the effect of projecting costs and health into the further. In the base case, we estimated using modeling, the post trial costs and DALYs of our per-person who avert death during the trial, due to their expected years of life after that. When we repeated the analysis with no assumptions about post-trial costs and health, the cost per DALY averted per arm A versus arm B, increased to almost \$12,000.00; and the cost per DALY averted on arm B versus arm C stayed about the same. The cost effectiveness ranking was the

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same with the sensitivity analysis, but more pronounced. Next slide please.

In conclusion, we found, with this trial, that adding CD4 to clinical monitoring at a cost of \$831.00 to \$838.00 per DALY averted is about as cost effective as putting another person on ART in Tororo, which we've separately estimated at about \$600.00 per DALY. We also found that adding viral load to the CD4 and clinical monitoring has a cost per DALY averted between \$3,600.00 and nearly \$12,000.00 which is 4 to 20 times higher than the cost per DALY averted for CD4. This analysis suggests that CD4 monitoring or starting a patient on ART are economically preferable to viral load monitoring, at least in the context of this trial. Thank you. [Applause]

**MALE SPEAKER 1:** Thank you Jim. Charlie will present, Charlie Gilks is from WHO and he is going to present another very important study still ongoing, called DOT, on which will add to what has presented so far. Charlie.

**CHARLIE GILKS, M.D.:** Thank you very much Peter, and I'm presenting this on behalf of the DOT trial team and I recognize Peter is one of the PI's in this. DOT, as I think most of you will know here is the largest treatment trial in Africa and indeed, with the premature closure of SMART it is fast coming the largest treatment trial in the world. This is

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an equivalence trial of treatment monitoring strategies in Africa. Could I have the next slide.

This is a clinical end-point trial. It was a long time in gestation, and indeed, we started designing the trial back in 1998. The recruitment started in 2003, so there was a five year gestation period. Remember, it was planned a long time ago and many things have changed in that period, so please be kind to us on the trial design.

The first two major interventions were the treatment monitoring strategy, I'll describe that a little bit more later, a structure treatment interruption, which was prematurely terminated on the advice of the Data Safety Monitoring Board on the release of the SMART data, and more recently, management intervention evaluating a simplification strategy and second line. The study was originally funded through the end of 2007, because of the success and the low event rates and the low mortality that we've seen, we requested and were granted an extension until the middle of 2009.

We've recruited over 3,300 patients, the majority of taking triple NRTI first line, 84-percent, 15-percent are taking a more expanded first line NRTI and NRTI regimen. So far, we've got about a 3-percent annual switch rate after the first year, so, meaning about 360 patients have switched, and

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they are going to go into two randomizations to optimize the background of the regimen to support a boost in protease inhibitor, and we will also be evaluation, in a pilot, boost in protease inhibitor monotherapy. Next slide please.

DOT is a multicentered trial, it's got three sites in Africa, three centers in Africa, JCLC which Peter's the PI for the MRC Uganda Virus Research Institute site in Tabee for which [inaudible] is the PI and the University of Zambabway site in Harraha in which James [inaudible] is the PI. About 1,000 patients to 1,200 patients in each site, and there is also a smaller arm managed out of JCLC Academic Alliance in [inaudible] in which has about 300 patients. There are two sites in the UK, the clinical trials in MRC and the Imperial College in the UK, and I should say that I'm presenting this, not as a WHO staff member, but this recognizes my association as a principal investigator in DOT, way before I was ever staff member in WHO.

We receive funding from three sources, Rockefeller, MRC and the UK Department of International Development and all the drug in the trial is donated either by Glaxo [inaudible] and most recently Abbott for the Kaletra or the lopinavir. Next please.

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Focusing down more on the clinical monitoring versus laboratory monitoring protocol, at entry and after initial screening for fitness to participate in the trial, in terms of clinical ability to participate, individuals are randomized either to clinical and laboratory monitoring, and in our case, this is CD4 supported monitoring, it does not include any virological monitoring, although plasma samples are stored and archived and are retrospectively reviewed by a sub studies. The other arm is clinical monitoring alone.

Both arms, the entry criteria is the CD4 count below 200. In the clinical monitoring alone, results are available if requested by the clinical officer looking after that patient, for specified reasons, or, if on independent laboratory review, a grade for toxicity is identified. In the clinical and laboratory monitoring arms, CD4 counts are reviewed and seen at entry, week 4 and week 12, and then 12 weekly or 3 monthly after that, and regular and biochemical and hematological results also returned.

The efficacy of the trial, the efficacy end point is progression to a new WHO stage 4 event, or death. We're following up patients, up to six years now, with the trial extension, and we've seen a 3-percent lost [inaudible] annually, and we are now reporting a 10-percent annual

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progression, either to Stage 4 or death. The initial sample size calculations were down to 15-percent annual progressions. As a non-inferiority, or equivalence study, we are powered with a stand at 80-percent and 5-percent alpha to demonstrate equivalence with the definition of 10-percent our event rate, plus or minus 1.8-percent, on 18-percent difference on that. IEA has a ration of 1.18.

I have two slides, to explain a little bit later on, the difference between the difference, sorry, inferiority and non-inferiority trials, just so that the audience who is not familiar with this subtle, but very important, distinctions can be away and why these differences exist, and critically what they mean.

In terms of the baseline characteristics in comparing it to the HBAC trial, we saw a similar number of women, 2/3 being recruited, slightly older, 37 years. The patients, by and large, were more immunosuppressed. We have a lot of catch up in all the three different sites in all of those three sites, of certainly, two of the sites that DOT was the first major implementer of antiretroviral therapy, so the median CD4 count was 86. One quarter of that patients already where in Stage 4 WHO disease, and the median viral load was about 280,000 copies. That was done in a smaller subset of patients

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in the virology study, about 300 patients right across the three sites, and that copy is about [inaudible] for log. This is, again, higher indicating more and more suppressed population HBAC, and then the other two indicators are as shown. Next please.

These are data that actually relatively old, but they've already been shown by a colleague from [inaudible] and they represent the survival benefit that we are seeing in DOT with basically triple new core, standard, first line therapy, and these data are extended out now to over three years, while I don't have a slide [inaudible] on my survival, it is out to three years. Essentially, and this complex slide is breaking down the survival by different CD4 strata at entry, and there are 4 CD4 stratas. 0 to 49 and so on and up to the low 200, and it compares in the heavy lines those who are in the DOT trial with matched cohort of patients followed in [inaudible] in a pre-ART evaluation, principally of polysaccharide pneumococcal vaccine but also of some other interventions.

Overall, at 2 years, we had 95-percent survival and at 3 years we had 94-percent survival. At two years, this represents an overall hazard reduction in death of 17 fold, so whatever the management strategy we using, and remember only half of those patients are being managed even with CD4 counts,

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we are seeing a spectacular impact on mortality and it's now out to 93-percent at three years.

Just now, two slide to explain the difference an inferiority trial and a non-inferiority trial. Remember HBAC was an inferiority trial. An inferiority trial recruits enough patients to show significantly sufficient differences in randomized groups and 95-percent confidence into who must one. Now the issue with this is, when you report say, a hazard ratio of 1.4 with a 95-percent confidence intervals of 1.05 to 1.87, while this is clearly, an inferiority has been demonstrated, the observable data are comparable between anything between a 5-percent and an 87-percent difference in the risks in those populations. They say they're different, but they don't tell you exactly how much these are, whereas a non-inferiority trial aims to recruits enough patients to show a statistically significant difference and to try to give you some sort of order as to how much difference that is. So, we have a 95-percent confidence interval around the treatment [inaudible]

The non-inferiority trial aims to recruit enough patients to demonstrate that the difference between the randomized groups, if any exists, is not very large. The 95-percent confidence interval around the treatment has to be small, and it can include one. So, in this, and [inaudible]

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has a ratio of 1.18, we are showing whether is this an up to 18-percent difference between the two arms, and we are powered to be confident and if we continue there is a less than 18-percent difference between the two management arms in terms of clinical, outcome, and death. Next slide please.

Final slide, to compare the differences between DOT and HBAC. We believe that the HBAC results are indeed, very reassuring for DOT. The viral suppression was high in all the harms in HBAC, and they note that adherence is very high and in DOT we are seeing and continue to see high and increasing levels of adherence over the years. We have a very, very adherent and very, very motivated patient population.

The death rates in HBAC across all their arms is similar, slightly higher, I would say, than the overall death rate in DOT, and there was slightly less immunosuppressed patients in HBAC. I think, in the absence of viral load and CD4 count, we can be happy [inaudible] clinical monitoring from HBAC suggesting that it is relatively safe, and certainly quite a cost effective intervention, and there are little differences in these arms.

We also believe, that at the moment, it would be sensible to avoid premature public health recommendations to WHO for ART monitoring based on one single inferiority trial

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alone and I'm glad to hear that Jono is going to be able to extend his trial to do non-inferiority for what we hope.

And finally, the DOT, and I would like to thank, very much, the principal investigator in HBAC for allowing our data safety monitoring board in DOT to share the data as they were coming off the press so that they could consider these data and what the implications were for our trial. I'm happy to say that our independent DSMB very carefully looked at the data and were happy for our DOT trial to continue as planned. Hopefully until the end, the middle of 2009.

Thank you very much.

**MALE SPEAKER 1:** Thank you. So we hand this over to the audience, there are two microphones and we have about ten minutes and then afterwards there's plenty of time to have some discussions with some presenters. Let's start, ladies first.

**VATA ELSOLDER:** Vata Elsolder [misspelled?], Columbia University, thank you very much for really very informative studies and I congratulate the investigators for tackling this very important tactical question. I have a question for Jono and for Jim. I'm particularly interested in comparison to arm A to B, because even small differences could make a big difference with the large number of individuals we're treating. I'm wondering, sort of, whether you feel confident from the

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sample size you had in HBAC to be able to— or can you tell us how you calculated the sample size and whether it was a primarily convenient sample and you just randomized the three arms, because I guess the question is, can we say with confidence that there's similar arms, A and B, based on the sample you have in your study. That's the first part of the question—

**MALE SPEAKER 1:** I think we will get some questions and then answer them afterwards.

**FEMALE SPEAKER 1:** And then the second question is for Jim, if most of the 50-percent of the death happened in the first three months, right, and that's remarkable, that's repeatedly shown in many different studies in Africa, and clearly monitoring would not have an impact on the early deaths because they happened really, before, before you could really do any of the monitoring in the study. If you excluded the early deaths, what would be the effect on DALYs, because you indicated that the deaths were really primarily due to the, the DALY, the [inaudible] DALY was primarily due to death. I'm just curious if you excluded those early deaths. Thank you.

**MALE SPEAKER 1:** Thank you. Next.

**PETER COWLEY:** Hi. Peter Cowley [misspelled?] from Uganda, I'm following up on some of the cost per DALY related

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calculations. I'm assuming a discount rate was used, and if so, what was the discount rate. I'm assuming discount rate was used in the calculation and if so, what was that discount rate. I'm also work under the assumption that some sort of productivity or some sort of age weighing applied to the DALY calculations, and I was wondering whether those were the standard ones that were applied, and the last question that relates to, I was wonder if, was there any difference in the time of, in the age of death, and how that relates to the DALY calculations in the worse case scenario. I imagine there could have been a lot of early aged deaths in one arm versus the other arm, and that would skew the DALY calculations, potential quite dramatically, and I'm wondering, was there any, gross differences in the age of deaths for among the three arms. Thank you.

**MALE SPEAKER 2:** Jono, I'm going to ask you a question about the clinical events in arm C. We talked about it before, but I think it's an important question for the audience, because, clearly the difference between arm C versus A and B has been driven by these clinical events, not my mortality, but by these events, and the interesting thing is that there seems to be a lot more events in arm C than there were switches. Now, I wonder why that is? Is that because of a perception by

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the clinician who didn't have access to CD4 viral load, that they weren't really that severe, or were they early events, such that the ART really hadn't kicked in yet?

**LEMAR HASBROCK:** Hello. I'm Lemar Hasbrock with US Government Team in Guiana, I had a comment. I think that as clinicians and physicians in particular, sometimes we get caught up in treating the laboratory values and not so much treating the patients, and we can kind of lose the forest for the trees, and I think that both of these studies kind of speak to the bigger question, which is, what we're all in this about, which is prolonging life expectancy and prolonging quality of life, and everything, all the benefits, that come with that so I think that both of these studies really answer a compelling question, what level of monitoring do we need, and it almost argues, in my mind, at least, for us to do very vigorous clinical monitoring, very vigorous adherence counseling, and then add the CD4. Viral load, we may not get much more bang for the buck, so in a perfect world, I don't think anybody would argue, but if we had our druthers, we'd do all three, but in a practical world with limited resources, these studies both make compelling arguments to do the clinical adherence very vigorously and add the CD4 monitoring. Thank you.

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**PHYLLIS CONKEY:** Hi. Phyllis Conkey from Harvard. I just have a, clarification point about the HBAC.

One is, I guess I'm confused if the purpose of the monitoring, whether it be clinical or laboratory, doesn't really result in the switch, so, and you had discordance in the different arms, so could you elaborate on why patients weren't switched.

And then, did you control for treatment of the OI's that were diagnosed?

And finally, I guess, how did you come to the conclusion that the lay worker quality of care was comparable to a qualified physician/nurse team prototype. Thanks.

**MALE SPEAKER 1:** Thank you. So let's go, we'll start with you Jono.

**JONO MERMIN, M.D.:** One of the risks of presenting preliminary results is that your colleagues think of new questions, so I'll answer the ones I can.

The first related to the same size calculations, we started this study a long time ago and we felt that, if we enrolled 1,000 people, which is about the limit of the funding that we had, that we would be able to determine differences that would have made a difference clinically, and as it turns out, there were fewer events than we had anticipated. People

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did better in the study than we had thought they might, so those calculations, which do exist, ended up, potentially, not giving us the results that we would have hoped for, except that, the difference did occur by the time we stopped the study and we saw arm C would have been stopped even if we hadn't reached the three year mark, I think, by the DSMB, because the difference was significant. So, the sample size was probably a choice of both funding and a result that would have made a difference to us if there weren't a difference among all three arms.

I think in terms of, there was a question come off about, how confident are we that arms A and B are similar, and I, it's hard to answer that, a lot of that depends on what kind of a difference makes a difference for you as a physician or as a policy maker. There are wide confidence intervals around the differences between arms A and B for new aids to finding illnesses and mortality, but, one knows, that for at least 330 people in each arm, that was not a significant difference, so one of the reasons we didn't find major differences might be because people adhered so well that events were less frequent than we thought after 3 to 6 months. So, that is why the idea of continuing this study, with arm C as re-randomized to arms A and B, so everyone's getting at least CD4 count monitoring. It

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will be use to see if people start to fail overtime, and we are seeing increasing failures using both of those criteria, it will be interesting to see what happens because power increases and on the utility of viral loads may also increase.

I think in terms of, Johan's in clinical terms of arm C and when did they occur, the non-mortal clinical events, almost all of them occurred in the first 3 to 6 months of therapy. Very few occurred later, in fact, most of our arm C clinical events occurred were mortal, people died [inaudible] and there are very few other events except for the ones that I mentioned. I haven't actually looked specifically, are there any arm C patients that had an AIDS defining illness during follow up and weren't changed. I can do that, but I assume it's actually fairly few.

Why weren't people switched depending on these, the criteria we had, again our first effort was always adherence monitoring. We wanted to provide the best care possible for the participants in the study and we didn't want to switch people to a second line regimen if it turns out it was an adherence issue. So, I think worldwide, people concentrate primarily on adherence, to try to improve the outcomes, ultimately for the patients, but also you're monitoring viral loads to try to suppress virus again. There was a recent study

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from MFS that showed, from South Africa, in Cape town that showed very nice results with a variety, in a fair number of people who had detectible viral loads when they went back after that viral load measurement and provided adherence counseling, about 70-percent or more ended up, again, having suppressed virus, so they didn't need to change so they concentrated on the others, so we had a tendency to do the same. We first counseled people and then we reassessed with the laboratory or clinical monitoring to see if they got better.

For clinical monitoring, obviously, if that's all you have, and they had a major illness, we couldn't do that. You wouldn't want to wait, you would just switch them and that's why we've had a number of people who were switched to second-line regimens after an AIDS defining illness.

And then, the assumption that lay people did well, I think that the real issue, when we started this study, was concerns that ART would have difficult to being brought out to people in rural areas, because transport is so difficult because people are poor, and because the health facilities didn't have the capacity, necessarily, to have enough doctors and nurses to treat patients, and that's obviously a concern for many of us today. What we wanted to do is to see if you had a lay person who was trained to detect early episodes that

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might be either toxicity or early failure and then encourage those people to come to the clinic for treatment so that the total number of visits to the doctors and nurses might be less, but that people would still see doctors and nurses if they had a serious illness. It's not that lay people substituted for a clinician viewing somebody who had potential toxicity or failure, it was that their delivery of drugs showed very high adherence, very low detectable virus, and very good responses in terms of mortality and CD4 cell counts. People still did end up coming to the clinic when they had symptoms.

I think that's it for me, and Jim, I think you had a question on cost effectiveness.

**JIM KAHN, M.D.:** Here we go. There are a few questions that relate to the cost effectiveness, concerning statistical power, just to expand on what Jono said with regards to the cost effectiveness, we treated some of the observed differences that did not reach statistical significance as real difference, not the less, so, the somewhat, underpowered level of the study didn't affect our ability to look at differences, we just treated them as significant. However, of course, it did affect the precision of those estimates and as more data come in, we can refine that.

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The per protocol analysis which excluded the first 90 days and about 45-percent of the deaths, would have shown fewer DALY gains, but the biggest change was that many of the arm B deaths occurred in the first 45 days, so in the per protocol analysis, arm A and arm B look very similar, and arm B is much better than arm C. We have not done that analysis yet, but I think it will look pretty similar when comparing arm B and arm C and viral load will look not at all cost effective because of its equivalence with arm B in that analysis.

The DALYs were just counted at 3-percent. We, in calculating future costs, we did do age weighting of disability, based on the average age of people in this cohort. We did not adjust for the age at death, if Jono knows anything about age of death within this cohort, maybe he could comment on that.

**MALE SPEAKER 2:** I would just like to comment with my WHO hat on here, about these definitions of failure. We found it very difficult when we did the 2006 guidelines, to come up with any evidence that really informed what failure was. We were quite careful in the text, there is no WHO definition, there are suggestions that you can identify failure clinically, immunologically or virologically, and we tried to state, quite clearly, we believe all of these three separate failures are

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different things, so I think it's not surprising when you try to correlate CD4 failure with viral load failure, the, find it quite difficult to get good correlations between the two because I think they're probably measuring different things. The difficulty that remains for us is whether we recommend strategies to identify early failure, or late failure. Ultimately we really don't know the consequences of early failure versus late failure in terms of what could be called premature switching to second line, or an appropriate time to switch to second line, and critically, the impact of an early or a late switch on the durability and the outcome of second-line therapy. The studies are not out there, the public health approach that most, all low-income, and most middle-income countries have adopted is very clear of [inaudible] first line, second line, nothing. That means that the critical question around when to switch is really very, very important and we don't have enough data to inform it.

We are beginning to talk about early versus late because, I think, clinically, we can start to suggest there are different clinical indicators of early or late. I think clearly there are some early or later indicators of virological failure and probably there are with CD4, but I think CD4 is difficult. Clearly, if you were going to put your money,

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unfortunately, you would want to buy viral load monitoring to identify failure rather than CD4. I think CD4 is very, very important for initiation of therapy.

**MALE SPEAKER 1:** Anyone with any comments? Well, Dr. Manmago you have something? Please come to—

**MATT BARNHART:** This is Matt Barnhart from USE, I have a quick question about whether anyone has considered using, since what you're looking for with virological failure, you don't necessarily need a quantitative result, something like dry blood spots testing, or some variant of that, because of the logistic feasibility?

**MALE SPEAKER 3:** My question is addressed to the first speaker. The talks of early and late failures and [inaudible] the fact the causes are too many. [inaudible] your patient you are giving me chemotherapy, then after a month you conclude this is inferior, so I'd like to be given some clarification what factors do you consider to call this inferior?

**MALE SPEAKER 1:** Charlie, I think you could answer that one.

**CHARLIE GILKS, M.D.:** Yes. Thank you for that question. [Interposing] I think individuals interpret an early failure as a low virological, where adherence has been guaranteed, okay, that's the first thing, the way you have

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continued viral at a level of 400, 1,000, maybe at 5,000, and people would talk about a later virological failure when somebody has had suppressed virus for months, maybe a couple of years even when it's around 5, 10, 50,000. We don't know because we haven't defined these. I'm just saying that people are beginning to consenturalize this around early versus late. We have no definitions around them, we have no evidence, but increasingly, when we are trying to think about it, that is how we are moving our thoughts around it. I will emphasize, we do not have definitions. The thicker of 10,000 in the WHO guidance came up was expert opinion. We did a strong poll of the 25 experts we had, and people range from 40 to 100,000, is the definition of virological failure, there are no data out there, this is individual informed opinion only.

**MALE SPEAKER 3:** Somehow, someone had said was you are [inaudible] the patient, if you know your patient, and the patient is adhering and you know the drugs you are giving and he is taking the drugs, I don't see how he can fail. [inaudible] If the failure to come later, the drugs become resistant. Because they become resistant overnight, so, we have to consider the patient. The [inaudible] of the patient is the patient [inaudible] or not. I think we should say, conclude, [inaudible] failure loads knowing why the patient is

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failing to respond, or the virus is not responding to the drugs. You see that as [inaudible] [inaudible] CD4. As I said earlier, the CD4 is a test which is very complicated, it is suppressed by [inaudible] injections and the edge itself, someone [inaudible] CD4 may increase gradually [inaudible] a constant match. [inaudible], we review, how are things going, [inaudible] oh, this patients is having [inaudible] and other things, or TB, so there are many factors that we have to consider. Thank you.

**MALE SPEAKER 1:** Thank you Dr. Elego [misspelled?], for that and I think with that comment, we want to bring this session to the end. We want to fast cover, I want to fast cover, just one moment, you want to make one last comment? Yes, certainly, go ahead.

**MALE SPEAKER 4:** I just have a last question for the last presenters. So I think this presents very interesting data, very promising, they are indeed preliminaries, we will have to wait for the final data, on the other side, we have the few presentations which have somehow different conclusions, which come from different settings. I think they're more abrasion settings, maybe currently the real life situation. I think it remains [inaudible] to wait for the final results of this study, but do you also consider, like an effectiveness

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study, because maybe in these conditions, the study, as applied, can be very promising and I think that it shows that if you have excellent adherence, the need of viral load is much less, but in real life, we have limits in human resources and other restraints. To what extent will you also evaluate whether the results will apply also in these settings, so to what extents will be generalized more?

Thank you.

**MALE SPEAKER 1:** Jim, you want to say something?

**JIM KAHN, M.D.:** It's an excellent observation and I completely agree with it, the settings are different, and I would also propose that some of the methods we used are a bit different and it would make a lot of sense, and I hope that we can do this, to apply some similar methods to the different settings so that we can disentangle our different method approaches from the differences in what may be a more research setting versus a more problematic setting.

**MALE SPEAKER 5:** Thanks, I just wanted to add one thing, actually, we did, I think one difference is that some of the earlier presentations focused on virologic outcomes as, and we were focusing on morbidity and mortality. We did actually do a very similar analysis to the three earlier presenters and found extremely similar results in the same context, so that

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CD4 counts very poorly predicted viral loads, they were both insensitive and non specific, so the question that I think those of us involved in the study that I'm involved with have been grappling with is, we know CD4 counts don't predict viral loads very well, yet in our study, CD4 counts did very well in terms of clinical outcomes, and the question that I think it raises for all of us is, normally we have a supremacy of viral load. If you have a suppressed viral load, even if your CD4 count is not doing very well or you have opportunistic illnesses, we still don't change people to second line regimens. In Africa we are not doing resistance testing, and probably couldn't do resistance testing because we couldn't detect the virus. On the other hand, we saw, could it be that CD4 counts are actually, an immunological assessment, is detecting something, as Charlie hinted at, something different, and we may have to start thinking about a combination of respect for both CD4 counts and viral loads that might then, in combination, provide us with even better clinical outcomes, the problem with going to that point is that we would then need to have clinical outcomes as the measure of interest and people raise questions about whether that's something we should be doing in the ethics of that kind of outcome.

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**MALE SPEAKER 1:** Yes, absolutely, let's have these, Kevin, you are going to do the [inaudible]?

**MALE SPEAKER 6:** Congratulation on a very fascinating session, but I mean, if there was more time, I'd love to ask each participant, what's the take-away message of all of this? But my take-away message is that this is all terribly reminiscent of what's happened over the course of the epidemic, in that, you know, we are comparing here cross-sectional data and cohort data, we're comparing observational studies and randomized control trials and we're talking about clinical end points versus surrogate markers, and none of that is new. It's been beddedding the discussion over the last 15 years, it was around the ART was being initiated, the Concord trial, and everything else. I think the lesson I take away from this is, if there's 30 billion dollars from the USG and another 30 from the G8, we better get this right, and the only way to get it right, if you don't know, is to do big randomized controlled trials.

**MALE SPEAKER 1:** On that note, Kevin, I think we'll end this session. Please join [inaudible] for the presenters. [Applause] and I thank the audience, you've been great. Thank you very much indeed.

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