

**2007 HIV/AIDS Implementers' Meeting:
Current and Future Challenges in Antiretroviral Treatment
Scale-Up:
Current and Future Challenges in ART Scale-Up
PEPFAR, The Global Fund to Fight AIDS, Tuberculosis
and Malaria, UNAIDS, UNICEF, The World Bank, WHO, GNP+
June 16, 2007**

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[START RECORDING]

JONATHON SIMON, M.P.H., D.SC.: ... it's well documented on both worker performance, on the labor fostich [misspelled?] firms have and in fact, in an earlier study in the same population, we documented sort of the natural history of productivity decline, unfortunately leading to death because we were doing it in the age prior to treatment.

We were quite fortunate in this situation that the same cohort, the same population of workers in Western Kenya, became one of the early PEPFAR treatment rollout sites in the private sector.

Now, the medical effectiveness is clearly well established. But very little is actually known in a deep, empirical way about the extent to which ART actually mitigates the impact of HIV on work performance.

And it's that question which drove this study, which was to estimate the differences in HIV-infected workers on ART and the general population of tea pluckers on days spent plucking, how effective they were, how productive they were on the days that they were plucking tea, how often they were shifted to what's called light duty, or being physically unable to do the strenuous work of plucking. And then, because we have a direct measure of productivity in the wage

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of a tea plucker, we're able to get an empirical estimate of total earnings.

Now, this is done in the tea estates of Western Kenya, which I showed you, in Kericho. Now these are large estates. They've more than 10,000 permanent workers. They are mostly housed on the tea company estates, and the tea companies are really agro-industrial concerns that provide their own health care system also.

Prevalence in this population was estimated about 14-percent in 2004 and, as I mentioned in April 2004, the company hospitals became some of the early private-sector treatment rollout sites via some PEPFAR programming.

So our studied population of the permanent employed tea pluckers, who were hired prior to 2002, and we have 59 workers who are on antiretroviral therapy and initiated therapy as part of the early cohort.

All of them consented to participate and allow both to look at their payroll data and their health data. We have a large control population, a reference population, which is over 2,000 workers who operate in the same work gangs.

And the reason this is important is it allows us to control for all the ecologic variation that you would have on

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productivity on the age of the field, the flush of the tea, some of the agriculture parameters.

Now, the study design is a two-directional, or ambidirectional, cohort study, where we went backwards two years prior, to the initiation of therapy, and we will follow this cohort out for three years post-initiation of therapy. The data that I'll show you today is the first-year data. This study is ongoing.

And what is the unique opportunity of this study, is actually remarkably simple. We linked two data sets that had been previously never been linked. We linked the payroll data set, which gives us a direct measure of labor productivity, and we linked it to the medical records that these agro-industrial states keep on their workers.

So in essence, through the worker ID number, we are able to construct a link data set that allowed us to do what the devils a lot of this work on productivity and health, which is to link medical records with direct measures of productivity.

For each subject, we have currently at least 37 months of data. As I said, this is ongoing. This report is on the first year of post-initiation of therapy.

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We had four specific outcome measures we were interested in, the number of days that tea pluckers were able to pluck per month, that's labor force participation information. Then we're able to get their daily output of tea pluck during the time they're in the field, the number of days they were shifted to light duty, and we're able to aggregate it into an income.

Let me show you the four tea results slides. First, the study of population between reference and index subjects was no different in terms of age.

As we see in many places in the world, there are more women on treatment than on men, and that's true in this population also. They were employed the same amount of time and the median CD4 countless population is 145.

And other analyses, we will be able to link productivity with stage of disease because we have the biomedical and clinical records on this population also.

Now, here's the number of days spent plucking. And as you can see, in the months prior to initiation of therapy, the workers are working pretty much the same amount as the reference population.

But in about eight to 12 months prior to, you have a massive sort of crash in their ability to participate in the

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plucking operation in the labor force, leading to, at times, zero, which is the initiation of therapy, some information that their labor force participation is very, very limited.

They can't get out to the field, and with the initiation of therapy, look at the slope of that curve of recovery. There's a rapid increase in that slope as they come back up and are more productive as we go through here, right, and then in about eight months, it begins to plateau out a little bit.

Well, interestingly enough, on the days that the tea pluckers actually get into the field, there's no statistically significant difference in the quantity of leaves they pluck. Then, in fact, as you look through the whole period of time though, there is a slight decline in the unit productivity of the individual worker across the whole 36-month period.

In fact, it is not statistically significant throughout the whole period of time. Okay? And remember, this is on the days that they get into the fields, they're able to pluck. It just means that they're healthy enough to do it.

But what you'll see is that there's a tremendous use of what's called light duty, and shifting the worker out of

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the plucking activity into other things like pruning plants, sweeping up, doing other things which, although they have value to the firm, are not considered as key to the industrial concern and they don't generate as much income for the worker.

And if you total that all up, that's what it looks like from a household income point of view. That incomes are a little bit declined until about eight months prior to, and then you have an absolute income crash on these households, leading to initiation of therapy as they can get back into the labor force, a rapid increase.

But then what you'll see is that it begins to plateau after about six to eight months and the reference population, they're earning about 89- to 90-percent of the reference population's income at about 12 months.

In essence, there is what looks to be an ongoing deficit of about 10-percent in labor productivity. Let me quickly go to some conclusions.

We've been able to show in this deeply empirical piece of work that there is a substantial and rapid improvement in the labor productivity in the first 12 months post-initiation of ART, both in terms of attendance, getting them back into the field and basically, having that income

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recovery, which is really crucial to the workers' point of view.

But unfortunately, we're not seeing a recovery all the way to the pre-morbid state. And in fact, there appears to be a plateauing of productivity at about 10-percent fewer days in the field and about 16-percent less kilograms of leaf plucked.

Now remember that what would have happened had there not been treatment, is that these workers would have died, and that's the earlier study that we published on. So from a household point of view, this is a fabulous outcome. And retaining a 90-percent of work force performance can only be seen as a tremendous success.

Now, this study has a relatively small sample size of the 59 index workers. We will continue it out to three years. There's much more work we can do with this cohort because we have the linked productivity and clinical data set.

But in essence, we believe that the benefits that we're showing are probably underestimates because of a process of use of helper workers, which sick workers tend to preferentially use and because, in fact, the reference population probably has some unknown HIV embedded in it.

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But the implications for the employers are actually quite different. Although it allows the HIV-positive workers to survive, remain in the work force and begin to work productively again, it isn't yet clear whether from industrial point of view, the value of the treatment actually exceeds the costs.

And I think one of the things to bear in mind as we celebrate this success of the treatment initiative, that from the point of view of the managers of the tea estates, they're asking a very different question, or two questions.

One, they're asking the question, why are we waiting until CD4 of 200 to initiate therapy? If I initiate therapy much earlier in the process, will I avoid that productivity decline?

And the second question that they're asking is, if it is illegal to terminate a worker because of his or her HIV status, is it legal to terminate a worker if I find that they are fundamentally underperforming relative to other workers through time?

And what will be the cumulative effect of more and more of my work force being on treatment, but potentially being at less than 100-percent of labor productivity?

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And I think that it is important as we look at this work, to not only look at it from the point of view of the individual worker and his or her family, but if we are going to expect the private sector to continue to support treatment, and if we hope that the private sector will assume treatment because of the cost benefit, we'll have to deal with some of these issues about productivity and the cost to the firm. Thank you very much.

[Applause]

KEVIN: Okay, we have five minutes for questions. Dr. Jiltz [misspelled?], I'm not sure of what the microphone situation is. Do we have a microphone to ask the questions?

Why don't you come up to the front, Charlie, while we're waiting to sort that out? This is Dr. Charlie Jiltz, by the way.

DR. CHARLIE JILTZ: Charlie Jiltz with WHO. Thanks, it's a very interesting presentation. I'd like to come back to what the initiation guidelines were for these tea workers.

I'm very impressed that their health and productivity crashed before they were started on treatment. And I think it's indicating that this was probably a clinical decision to initiate when people were already sick.

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I don't think it's the CD4 less than 200 issue. I think it is probably around people starting when they're sick, and I think it just confirms from a labor-productivity point of view that we're starting people too late.

JONATHON SIMON, M.P.H., D.SC.: I would agree that it was a clinical definition of one to initiate therapy. There are CD4s on this work force and some of them have multiple readings of it because they are in care thing. But clearly, from a labor force-productivity point of view, we're waiting far too late to initiate therapy. I fully agree.

KEVIN: Other questions? Any other questions, please walk to the lady with the microphone. Okay, if there's no further questions...

JONATHON SIMON, M.P.H., D.SC.: Thank you.

KEVIN: Then I think we'll go to the next presentation. Thank you very much, Jonathon.

[Applause]

"The next presentation is by Dr. Son Nguyen from CDC Vietnam, and the title is Early Outcomes of Antiretroviral Therapy Implementation in Ho Chi Minh City, Vietnam."

SON NGUYEN: Good afternoon. Today I would like to present a study titled, "Early Outcomes of Antiretroviral Therapy Implementation in District Four, Ho Chi Minh City,

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Vietnam." The purpose of this study is to present one of the first baseline data of the ARV patient at district outpatient in Ho Chi Minh City, Vietnam.

In this slide, you can see some HIV data in Vietnam. On average, more than 100 Vietnamese get infected with HIV every day and HIV prevalence in Ho Chi Minh City is higher than the national prevalence. This is 1.2-percent as compared to .05-percent of national level. And the estimated HIV cases in Vietnam are 280,000, of which proportion of HIV patients who are rejecting [inaudible] is 56-percent.

And then I would like to talk about HIV in District Four. In general, District Four is a poor district in terms of the low socioeconomic status, and this also has a high density of IDU. Since 2004, more than 1,000 IDU has irradiated and sent to the drug rehabilitation center. In addition, 22-percent of the total HIV cases in District Four are IDU. And in Ho Chi Minh City, there are 19 HIV clinics and District Four is one of most crowded clinics at the district level. This accounts for 13-percent of total ARV patients in Ho Chi Minh City.

And then we talk about the desire in retro [misspelled?]. We developed the data obstruction of [inaudible] patient money indicator to collect the data.

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And we when we did a restore [inaudible] review of 391 patients' charts with at least treatment, ART, between September 2005 to September 2006. And we also conducted an interview of the outpatient staff, and the data was entered into Epi Info and analyzed with SPSS.

And this slide saw some results of the demographic characteristic of the patient, 80-percent are male, and the mean of age are 29.5 years. Regarding the residence, only 38-percent resident of District Four, and 52-percent from other Districts of Ho Chi Minh City, especially 10-percent coming from other provinces up to 500 km away.

And this is a result of the baseline characteristic of the patient. You can see 20-percent of patients have a past history of ART, and the patient is sick with 78-percent presenting in [inaudible] stage III and IV, and over 50-percent with CD4 count less than 50.

And the high percentage of anti-HIV-positive suggesting history of IDU is a 72-percent as compared to 29-percent of patients in the city hospital. And in addition, 20-percent of the patients get infected with HIV at BBICB and TB. They suffer the Atripla infections.

This is the very last HIV regimen of the patient, and this regimen is inconsistent with the MOS and the Ministry of

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Pow Gi Li [misspelled?]. However, the use of the Neviraprine [misspelled?] in this population of patients with HCV infection has been raised as a concern, in terms of adverse events and hepatitis progressions.

And this is mortality rate and a loss to follow-up the patient. The early mortality rate is consistent with our other district clinic in Ho Chi Minh City and consistent with the sick population. And this led to an institution of the fast-track ART protocol earlier [AUDIO BREAK] - rehabilitation center. And one other major finding is the patient living outside District Four accounting for 50-percent of loss to follow-up and some lesson learned.

The first, firstly, combination of refuse and long-distance travel to base a living outside District Four would be a barrier to treatment adherence, and long-term treatment success. And our recommendation is strengthen treatment support network, and try to link the outpatient clinic to the CBO and family members to enhance the appearance and improve the patient tracking.

Secondly, high demand for ART and [inaudible] result in difficulty to recruit and retain full-time staff, adequate clinical [inaudible] also site an issue. And our

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recommendation is that government needs to commit to stopping plan and quality assurance measures.

Another lesson learned is HCV co-infection and subsequent side effects did not seem to be a factor in loss to follow-up. But we recommend that the long-term outcome of HIV and HCV patients treated with Neviraprine should be a set. And we see that the loss to follow-up investigation reviews apparent loss to follow-up by 50-percent and resolving in a protracting measure at the outpatient clinic, and our recommendation is maintain and improve the metric to prevent a true loss to follow-up and implement it in the clinic.

So that's it. My presentation and I would like to acknowledge my partners and colleagues at Ho Chi Minh City providence community, CDC Vietnam, District Four and staff and patients. Thank you.

[Applause]

KEVIN: Thank you, Dr. Nguyen. Questions on this presentation? Over there, could you please come to the middle? Could you come to the middle quickly, and meet the lady with the microphone?

ELIZABETH [misspelled?]: Good afternoon. My name is Elizabeth. I am from Kenya. I work with International

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Community of Women with HIV/AIDS, and I'll maybe take us back a little. I would like to ask the gentleman who was presenting from Kericho.

He had talked about most women being the ones infected by HIV, but that seemed not to be clear for other things other than a talk of things PAP smears and a follow-up on sexual reproductive, whatever. So I think if I could get a little bit of clarity on that.

And again, from the presentation that we just had about ARVs, I would like to know what type of ARVs most patients are using? Are they first-line or second-line? Are they working? What is not working?

And from the recommendation that people put ARVs when their city falls below 200, is that to add [inaudible] to stop that, or is that something that needs to be done after that? So, I'll just let you answer that.

KEVIN: Thank you, can I suggest that you, as far as the Kericho question is concerned, that you discuss it afterwards, since that presentation has gone and we're short of time? Dr. Nguyen. Did you hear the question?

SON NGUYEN: No.

KEVIN: The question was, could what proportion of your patients were on second-line therapy?

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SON NGUYEN: 0.13-percent in the second line. In the 391 patients, we only have one patient on the second-line regimen.

KEVIN: And the other part of the question was, do you have any insight into treatment failure?

SON NGUYEN: Yeah, because Vietnam just started ARV treatments in September 2005, and we begin looking at the treatment failure now, and in next month we will do vital log and genotype to identify the treatment failure and record of resistance in Vietnam.

KEVIN: Okay, any other questions for Vietnam? Okay, thank you, Dr. Nguyen.

[Applause]

The third presentation is by Dr. Willy Were from the CDC group in Uganda, "Clinical Toxicity to Highly Active Antiretroviral Therapy in a Home-Based AIDS Care Program in Rural Uganda."

WILLY WERE, M.B., CH.B., M.SC.: Ladies and gentlemen, I'm pleased to present to you our finding in the evolution of Clinical Toxicity of HIV/AIDS Care Program in Eastern Uganda.

I'll adhere first to the first 18 months of the ART program. It is a world that [inaudible] now that ART

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prolongs life and saves life among people living with HIV/AIDS. And that ART start rapidly expanding in Southern Africa. A number of toxicity levels have been associated with ART, for instance, studies are suited with paper [inaudible] and as eratticonosis [misspelled?].

Neviraprine is associated with skin rash and hypertoxicity. However, [inaudible] on these toxicities is well described in the industrialized world, very little information is available in the infants' ART programs in Africa.

In this study, with this [inaudible] clinical toxicity as associated with ART, the Home AIDS Care project in rural Eastern Uganda. In the Home-Based AIDS Care project, that I'll refer to as HBAC, adult [inaudible] on the AIDS support of an addition [inaudible] are enrolled for ART.

ART eligibility in city for [inaudible] for advanced HIV disease of stage III or IV. This analysis is linked to [inaudible] patients enrolled between May 2003 and December 2004. These were patients who had started on the first-line regimen [inaudible] studied in Lamivudine, Neviraprine or Efavirenz, depending on whether they referred or not. They also were provided prophylactic and [inaudible] treatment where indicated and supportive care.

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In HBAC, at initial contact, studies tradition to conduct thorough [inaudible] examination and [inaudible] evaluation, that includes HIV viral load, CD4 cell count, complete blood count, and liver and renal functional tests.

Once the patient is enrolled with ART, qualifies for ART, welfare workers deliver all the medications to the patient at their home during weekly home visits.

During those visits, the welfare workers, using standardized forms, provide adherence and support, assess potential symptoms of ART failure or toxicity such as fever, jaundice, numbness, rash, new cause of inflammation, loss of weight and others. Welfare workers also provide feedback to medicals and if a patient [inaudible] with expected toxicity or severe illness. Many times, they will contact the medical staff using mobile phones.

Toxicities is considered in this analysis were those that were clinical [inaudible] and confound by [inaudible], not those that were determined by the [inaudible].

The [inaudible] or the toxicity that followed the 1992 [inaudible] as indicated in this slide. Severe toxicity was that of [inaudible] grade III or IV, or [inaudible], hypersensitivity, anemia, acute hepatitis, pancreatitis or death.

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We use a couple of [inaudible] of analysis to determine time to first occurrence of anti-toxicity, time to first occurrence of on severe toxicity, time to first toxicity related single-drug chain, and also we used inverted and much averted [inaudible] monitoring to determine a sensational selected independent variables with occurrential [misspelled?] toxicity.

After enrollment, most patients were females. The median age was 38 years. The media CD4 cell count was 136. Median viral load was 220 copies. So generally, they are very sick patients, 96-percent of the patients were started on the therapy, and only 4-percent on Efavirenz. Eight-percent of the patients had had TB treatment before.

In all, [Inaudible] were the commonest toxicity rated five. Forty-percent of the patients reported some toxicity at one stage, and only 14-percent developed severe toxicity. Therefore, severe toxicities were not very common in this population.

[Inaudible] toxicity by 10, by 18 months the people remaining free from any toxicity was 0.47. And that means that slightly over 50-percent of patients had developed any toxicity.

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But only 14-percent had developed severe toxicity by 18 months. The instance of any toxicity was 4.5 per 100 of observation of person's years of observation, and of severe toxicity 1.3 per 100 years of observation.

In my [inaudible] analysis, we looked at gender, body mass index, age, CD4 and history of CV treatment as a predictor of toxicity. And we saw that age of 35 years older was most significantly associated with any toxicity.

Patients in that category of age were about [inaudible] twice, more likely to draw any toxicity compared to those who were younger.

Looking at neuropathy, the commonest toxicity, patients age that are 35 years or older were all twice more likely to develop any toxicity. And the same age group of patients were times more likely to develop severe neuropathy than the younger ones. Patients who have treated for TB were also more likely to develop severe neuropathy. This latter could not have been attributed [inaudible] in TB treatment.

Looking at single-drug substitution, by 18 months, we'll have substituted 220 [inaudible] substitutions. One hundred eighty-one of these - that is about 82-percent - were due to Stavudine and 17 due to Neviraprine. None was due to

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develop Lamivudine or Efavirenz. We didn't discontinue in patients because of toxicity.

We looked at the probable remaining three from any on the same regiment. By 18 months, over 70-percent of patients had not any drug substitution, meaning that the vast majority of patients were still on the first-line regimens, and those who had toxicity [inaudible].

By the finding, though, this evolution, well, that good, it said to have some indications. The toxicity that was unlikely here was not good to determine that [inaudible].

This could have been underestimated as some could have been missed since they were not determined by the [inaudible] evaluation. The commonest toxicity of neuropathy had lost [inaudible].

So the [inaudible] provided may have been [inaudible] in some cases. Some death could have occurred before the toxicity was determined, so that rose, of course, our underestimated.

To conclude, by saying that toxicities were common, but were a manageable condition. They were not [inaudible] to regimens containing Zidovudine, Lamivudine and Neviraprine. Neuropathy and rash were the commonest toxicities recorded.

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Age of 35 or older was associated increased hazard of toxicity, and to the closest treatment was also associated with an increased hazard or severe neuropathy.

We recommend that in the ART program in sub-Saharan Africa, attention should be paid to neuropathy especially age of 35 years or older and among those who are receiving TB treatment.

And since some toxicity occurred in about 40-percent of patients who [inaudible], there's need to expand formulary beyond the drugs current [inaudible] for [inaudible]. I recommended a contribution of those individuals and organizations and that is the [Inaudible] that can go forth.

[Applause]

KEVIN: Thank you very much, Dr. Were. Questions for this presentation? Where's the microphone? Could you please walk to the middle, so that you can all, if the lady with the microphone could stand still, everybody could go to her and that would probably easier.

FEMALE SPEAKER: Thank you very much. I would like to ask, I realized, I am [inaudible] from Uganda. I represent People Living with HIV/AIDS. I've realized they've been given those as door-to-door service to people living with HIV/AIDS as ART's consent.

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I want to ask whether they have been having any challenges in terms of stigmatization, because in Uganda, it would be quite difficult for us to have this kind of service, which is to me, is very good and easy to get closer to a person living with HIV.

WILLY WERE, M.B., CH.B., M.SC.: Yes, I want to say that the patients that we are treating are not from the general population. These are patients weren't having care and support at this organization, and they are most times disclosed.

Those who haven't disclosed, we did help them to disclose, but most of them are disclosed. But we do realize that with the kind of support we give them, the stigma is not a big problem.

DR. WALLACE PETE [misspelled?]: Thank you very much. My name is Dr. Wallace Pete from Catholic Relief Services in Kenya. I have two questions for you. The first question is, you work in a resource-limited setting. What is the rationale of being a baseline viral load in your patients?

Then two, in the amount variate analysis you found that age was an independent, was significant associated toxicity. Now, that sounds rather curious. Did you think about any other confounding factors to that association?

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Because it just doesn't seem logical that age can be linked to things like toxicity and rash.

WILLY WERE, M.B., CH.B., M.SC.: Using viral load is actually currently the recommended means of, where possible, of assessing people for antiviral therapies.

After this study of ours, this is part of a big study, we started looking at way that is [inaudible] only people on therapies, with viral load where they're picking [inaudible] in associated settings.

But as for baseline qualifications need, I think it's recommended the ideal. And because for the scientific study, we needed to have facts so that maybe we could even have [inaudible] how did you study them, but we did [inaudible] accurately, recommended that [inaudible] therapies.

The second question was... I forget, the second question?

DR. WALLACE PETE: The second question was the relationship with age between neuropathy and age.

WILLY WERE, M.B., CH.B., M.SC.: Neuropathy and age, I think has been described by others. This is not the first time, in the [inaudible] analysis we looked at several other things and came with that.

KEVIN: Dr. Von Frag [misspelled?]

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DR. VON FRAG: Yes, thank you, thank you for your interesting study. I was wondering in assessing toxicity at the home care level if you have any indication if those toxicities were captured at the clinic visits as well.

And I'm asking that because in Tanzania, we find that neurological examination is a skill which gets very easily lost in the follow-up after the initial training, and if there's difficulties to maintain basic neurological examination skills?

You did it at the home care level. But were those toxicities also already identified when the patients were visiting the clinics every month?

WILLY WERE, M.B., CH.B., M.SC.: The instrument that the field office had used for establishing neuropathy was a very simple one that only [inaudible] by numbness, tingling pains, or weakness of muscle, and then they would refer the patients to the ,medicals who would then do the final determination on staging of the [inaudible] determining.

KEVIN: If you want to ask a question, please go to the lady with the microphone. You go to her, please, rather than her coming to you.

MALE SPEAKER: My name is [inaudible]. I'm working for Columbia University. [Inaudible] presentation is

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[inaudible], the most common side effect of the antiretroviral therapy. Do you have any information that's related with the dose of D4T or [inaudible]?

WILLY WERE, M.B., CH.B., M.SC.: We looked at that, but D4T didn't have any difference in [inaudible] of neuropathy.

KEVIN: Okay, last question, I think.

MALE SPEAKER: Hello, you talked of this toxicity, which is a big problem. I wonder if you failed to find out in your combination of the [inaudible] and the [inaudible], which is weak, which is actually more toxic than the other one. Have you tried to shift that line to another line, or you think those drugs, the three of them equally toxic?

WILLY WERE, M.B., CH.B., M.SC.: No, the [inaudible] could not have studied that, because these drugs are given in combination of Zidovudine, Lamivudine and Neviraprine. So we just looked at the whole set therapy of the [inaudible]. But definitely, studies designed to look at [inaudible] establishes that [inaudible] associated with neuropathy then those others.

MALE SPEAKER: It seems so, because as HIV/AIDS commission, if you want to monitor your patients and then to

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give drugs like rats as if you are giving food, you should know which drugs is more trusted than the other one.

Even if the patient is suffering from neuropathy, you should say this neuropathy is mostly likely caused by Neviraprine or Staverdine. Staverdine is a drug of which we have abundant already, [Inaudible] is [inaudible] neuropathic.

WILLY WERE, M.B., CH.B., M.SC.: But I hope you know that [inaudible] combination for associated [inaudible] since 2003 that the first-line regimen is...

MALE SPEAKER: We are here to verify those drug which should be stopped. First, Staverdine is known for that. So if you have a combination of Staverdine and Lamivudine and Neviraprine, for sure your patient is going to develop [inaudible] lupus. Inevitably. So you don't give [inaudible], to Lamivudine. Lamivudine is [inaudible].

So here, I think you have to learn how to make combinations of drugs to shift from this line to this line, and where in this study, I mean in each study we have to know drug resistance, all right?

WILLY WERE, M.B., CH.B., M.SC.: Well, thank you very much. I think you're supporting me.

MALE SPEAKER: [Inaudible].

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WILLY WERE, M.B., CH.B., M.SC.: What we say is that we are thinking that [inaudible] is associate with neuropathy, and therefore we are recommending that WHO should recommend more [inaudible] what they are already given, so that..

KEVIN: Okay.

WILLY WERE, M.B., CH.B., M.SC.: ... [inaudible] can do [inaudible] better.

KEVIN: I think we, thank you that was an interesting debate and I think we can come back to it a bit later. But we need to move to the next presentation. So let me hand it over to Marylou [misspelled?]. Thank you.

[Applause]

MARYLOU: The next presentation is by John Idoko from Jos University Teaching Hospital. And the title of his presentation is "Hepatitis B Virus Co-Infection Impacts Baseline HIV Parameters and Heart Related Hepatotoxicity Risk in an HIV-Infected Nigerian Cohort."

JOHN IDOKO, M.D.: Good afternoon. I want to share with you some of the data that we have on the impact of hepatitis B, I am sorry, the impact of hepatitis B co-infection on a number of patients that we have been looking at in Nigeria.

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We have all seen that in the last 10 years, the use of HAART has tremendously benefitted our patients and improved the quality of their lives.

We have also seen that as a consequence of the use of HAART, opportunistic infections have declined in all our patients. However, it means that our patients are living longer, and therefore some of those of our common diseases, like hepatitis B and hepatitis C, become very significant as we manage these patients. We also have to bear in mind that many of the drugs that we use cannot with hepatic toxicity, et cetera and adverse effects in patients who are on these drugs.

So in the next 10 minutes, I want to share with you some of the data that we have from the patients that we've been looking at Nigeria, a core of our patients.

The PEPFAR program, they have a PEPFAR program in Nigeria, used to be in six sites who are now in nine sites. Our initial therapy has been the use of Stavardine, Lamivudine and Neviraprine, and we have baselined our patients at, start at six months, and in addition we've been able to carry out a [inaudible] of this [inaudible] and hepatitis C on our patients.

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The prevalence of hepatitis in Nigeria is between 11- and 21-percent in the general population. And this is why it becomes important in those patients who have HIV.

The prevalence of HIV in Nigeria, the prevalence of hepatitis B in patients infected with HIV in Nigeria varies from 11- to 75-percent, according to various reports.

We know that hepatitis BV includes the risk for error to related to [inaudible], there are a lot of studies that have shown this. But we do not know for sure whether this is the case, you know, in Nigeria and many other African countries. The effect of chronic hepatitis B on ARV response, therefore, is not clear and we know that there are very few studies, if any, in Africa.

So the hypotheses are risk factors involved, chronic hepatitis B, because it impacts the risk for hepatitis C and the effectiveness of HAART in this Nigerian province. The methods we used, all the patients received the drugs that I just mentioned at our site in Jos. Jos is like northeast of Abuja, for those of you who have some knowledge of Nigeria, 350 kilometers. They all start out with a drug regimen for HAART that I just mentioned, and we were able to carry hepatitis B and hepatitis C.

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And for this study, we were only interested in hepatitis B, so we were able to - all those who were hepatitis B negative were therefore chosen and therefore, we excluded those were hepatitis C positive.

We did [inaudible] antigen at baseline and then we counted for CD4 and [inaudible] HIV already, and the alkaline to [inaudible] at baseline three months and six months. And the outcome for this study was HIV already at baseline and then we wanted to see how many were below 200 copies at three and six months.

Similarly, we also wanted to see at six months how many patients had an increase of more than 50 cells [inaudible] millimeters of CD4. The third outcome was we were interested in hepatotoxicity and we're interested in, at the end of the study, those with outlined [inaudible] that are five times of the limit of normal, this was baseline was normal or 3.5 times the baseline if it was abnormal at baseline. Statistics were done during the [inaudible] tests and then we did use [inaudible] strip test or the [inaudible] test for category calibers.

Now this is the flow of the patients' results. We have 1,968 patients, out of which 336, 17.6-percent, were [inaudible] antigen positive, and 273 were anti-hepatitis C

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negative. And we were able to follow 262 of these patients, sufficient for the six months of the study.

The contributions were 1,682 who were [inaudible] antigen negative, and this will look at, and out of these, 1,361 were anti-HCV negative. So we ended up with a control figure of 1,305 [inaudible].

The demographic of patients is shown on top of this table, the mean age of the patients, as you can see, those who were co-infected were 34.4 and those who have only HIV was 35.5. And those who were HIV and [inaudible], an E antigen positive we have 63 of that, the mean age was 35. And for those who were co-infected but the antigens were negative were 33 years, we have 94 of that.

Sixty-three-percent of the patients were male, and you can see across the board if they are co-infected and 62-percent of those who were HIV-positive only were also males.

We almost had the same number if you separated those who were [inaudible] antigen A positive and also E antigen positive. These are [inaudible] those who have [inaudible] in negative and who are E antigen negative among those who were co-infected.

Ninety-percent of the patients were on Myrick [misspelled?]. Out of this 126, of the HIV positive were also

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on Myrick. And then you have between the E antigen positive and the E antigen negative 17- and 29-percents were infected.

Now, this is the [inaudible] median baseline of HIV already is clarified by HIV and [inaudible]. And as you can see if you look at those who have HIV only, they have a much lower baseline HIV [inaudible] compared to those who were co-infected.

And if you look at those who are co-infected and divided them all into those who were [inaudible] antigen positive and E antigen positive, as in most of the [inaudible] disease you find also that the HIV already at baseline was a lot more than those who were A antigen negative.

There were two [inaudible], how many of these patients in these various categories had AB [inaudible] to less than 200 copies, at three months and at six months. And it will take three months 65-percent of patients who were co-infected had viral load copies below 200.

That's against 68-percent of patients who only had one infection with HIV. Similarly if you look at those who were E antigen positive, 67-percent of them were able to reach undetectable levels of 200 copies at three months and then 60-percent of those are negative.

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Six months they're almost like all the same, hepatitis B co-infection 74-percent, HIV only 76-percent. And between positive and negative E antigens, you have 76-percent and 75-percent.

Now, what about a median CD4 counts stratified by HIV and [inaudible]? And as you can see there, you look at HIV only and then look at co-infected, you can see that HIV only have much higher CD4 counts at baseline. Six months later, six months later they all have very impressive [inaudible], more than 50-percent if you're looking at more than 50-percent rise, we have 75-percent in the co-infected and 73 in...

What about the providential [inaudible], as you can see clearly suddenly those who were co-infected as [inaudible] the blue, suddenly more contempt of [inaudible]. But I want to stress that you can see is only facts, if you look at the literature, a lot more emphasis [inaudible] from various parts of the world.

So my conclusions, B co-infection affects B-infection is common at Jos and all the parts of Nigeria, and hepatitis B co-infected who are E antigen positive have no CD4 count and highest HIV at any levels at baseline. However,

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hepatitis B co-infection in the first six months does not limit [inaudible].

And we have seen hepatotoxicity here, but the risks are much lower than what is reported. And we also want to add that this, as we become more proficient in the management of our patients, this is going to be a common [inaudible] that we'll look at, hepatitis B and [inaudible]. Thank you very much.

[Applause]

MARYLOU: Thank you very much. We can take questions. We have a microphone. Who's got the microphone, in the isle over here. Okay, no questions? Okay, great, thank you very much for the presentation.

JOHN IDOKO, M.D.: No questions?

[Applause]

MARYLOU: Okay, our next presentation is going to be presented by Marian Cauphana [misspelled?] from Massachusetts General Hospital, and she will be presenting "Antiretroviral Treatment Roll-Out In South Africa Alternative Scenarios And Outcomes."

MARIAN CAUPHANA: Good afternoon. South Africa has one of the largest burdens of HIV disease of the world, with and estimated 4.9 to 6.1 million people infected.

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It is estimated that 346,000 AIDS-related deaths occurred in 2005 alone. In 2004, the South African government began antiretroviral therapy rollouts, although the number of HIV patients in care in South Africa has been steadily increasing, and estimated 206,000 or fewer than 21-percent of those in need were in care by the end of 2005. with a plan from the South African government for 1.4 million total by 2008.

Our objective in this study were to examine alternative ART rollout scenarios in South Africa in order to first forecast the number of lives lost while awaiting therapy among treatment eligible patients, and the number of patients in treatment over the next several years.

Secondly, to project when total ART need would be met, and third, to form decisions regarding the life saving value of alternative treatments [inaudible] scenarios.

We use the cost effectiveness of preventing AIDS complications or C5 international model, this is a computer-based simulation model in which patients move through a series of health states that are reflective of HIV disease and treatment.

So this figure depicts the three general HIV disease states that are defined within the C5 international model.

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These are chronic infection, acute clinical events such as an opportunistic infection or drug-related toxicity, and death.

So patients enter the model with chronic infection as depicted in the upper left. In each month, they can either remain in the chronic stage or transition to an acute clinical advance or to death.

Patients, who transition to the acute stage may also return to the chronic HIV stage, develop another acute event in the following month or die. Within each stage, the model keeps track of CD4 cell counts, of HIV R&A, both current, on therapy on the set point, of antiretroviral therapy including the success and failure of first- and second-line therapy, the history of opportunistic infections and use of prophylactics, as well as treatment related toxicity.

So we use natural history and treatment efficacy data from South Africa [AUDIO BREAK], [inaudible] included, annual death rates for cohorts of treated and untreated patients eligible for ART.

Finally, we used information generated by the model to make projections of outcomes over the time horizon from 2005 to 2010. We chose to begin the analysis time horizon in 2005 as this is the year of the latest, most recent WHO estimates.

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So we examined four different growth scenarios for ART rollout, though these scenarios are not exact, they do reflect proposals made by the Actuarial Society of South Africa, ASSA and the South African Joint Task Team on HIV/AIDS.

These tragedies range from a zero growth scenario on top which provides 750,000 new treatment slots by 2010, to a rapid growth scenario which provides 2.8 million treatment slots by 2010.

This slide summarizes some key model info data, the first ART regimen efficacy that we used for an NNRTI with Zidovudine and 3TC. It included 84-percent viral suppression and CD4 increase of 184 cells at 48 weeks.

Our second regimen ART efficacy was for Lipinoveratonovere [misspelled?], again with the Zidovudine and 3TC, and included 70-percent viral suppression and a CD4 increase of 151 cells at 48 weeks.

We distinguished patients into two cohorts in this analysis. The prevalent cohort reflects patients who are already in need of therapy in 2005. These patients had a mean CD4 count of 92 cells at the beginning of the analysis time horizon.

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In contrast, the incident cohorts, seemingly patients from 2006 to 2010 who progress with HIV disease to required therapy. These patients had a mean CD4 count of 210 cells at the beginning of the analysis time horizon. The outcomes of both cohorts are effeminate for both the ART and no-ART strategies.

This results slide shows the percent of ART needs met by year in our projections. So on the horizontal axis, you have the year, and on the vertical axis the percent of ART need met.

All the scenarios begin with the same number of patients treated in 2005, and has the same percent of coverage and to then diverge into subsequent years. Treatment coverage under the zero growth scenario shown in white, peaks the in 2007 and then decreases steadily through 2010, at which time 45-percent of people in need of therapy will receive it.

In the constant growth scenario, shown in yellow, treatment rates steadily increase but still reach only 65-percent of necessary coverage by 2010. Both the moderate and the rapid growth scenarios shown in orange and purple, increased steadily and reached full treatment coverage in 2010 and 2008 respectively.

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This chart shows the projected deaths by year through 2010 for each scenario. In every year, as you can see, the number of deaths is greatest in the zero growth scenario, shown on the left and white.

Through the zero and constant growth scenarios, the number of deaths initially decreases through 2007 as treatment slots are added. It then increases in 2008 to 2010 as the number of eligible patients outpaces the number of new treatment slots.

However, in the rapid growth scenario, the number of deaths decreases dramatically from 2005 to 2007 due to the impact of ART, as you can see in purple on the right. By 2008 annual deaths begin to increase as patients who initiated ART several years earlier begin to fail therapy.

This table shows the number of AIDS deaths and patients alive on ART from 2005 to 2010, as we basically total the number of deaths for each year from the previous slide.

The number of AIDS deaths ranges from 2,197,000 in the zero growth scenario, down to 1,161,000 in the rapid growth scenario. The number of patients alive and receiving therapy ranges from 693,000 in the zero growth scenario to 2,572,000 in the rapid growth scenario.

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We conducted extensive sensitivity analyses to assess the impact of differences input parameters on our study results. I will focus on these parameters that had the biggest impact here. So these were the availability of CD4 counts monitoring, the number of ART regimens available, and prioritizing care for those that waited the longest.

So this shows the impact of the availability of CD4 monitoring on the number of deaths. In the absence of CD4 monitoring, decisions on treatment initiation switching are based solely on clinical criteria.

The number of AIDS deaths with CD4 monitoring available from 2005 to 2010 is the same as on the previous slide shown here on the left. The number of deaths with no CD4 monitoring available is substantially higher in every scenario.

In the zero growth scenario, deaths increased from 2,197,000 with CD4 monitoring to 2,455,000 with no CD4 monitoring. This effect, as you can see, is more pronounced than the rapid growth scenario where death increased from 1,161,000 with CD4 monitoring to 2,204,000 with no CD4 monitoring.

Overall, compared to corresponding scenarios where CD4 monitoring is available, the lack of CD4 monitoring

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results in 258,000 to 1,043,000 increased deaths. And some other sensitivity analysis just to go over quickly, we examined the impact on the results of having only one line of ART available so low perese [misspelled?] inhibitor. Under these assumptions, deaths by 2010 increased by 42 to 130,000, but the rapid growth scenario, still a minimized total deaths.

We also validated scenarios where ART is prioritized first to those who had been waiting the longest, effectively treating the sickest first, and doing so prevented an additional 50 to 114,000 deaths by 2010.

So this study had several limitations, first the model incorporated data from multiple sources, in order to address this we used the best available South African data and examined other inclines in sensitivity analyses.

Secondly, we did not address the cost and feasibility of the different model scenarios. The cost of doing this are critically important, but it was outside the scope of this analysis.

Third, while this study does not account for changes in the HIV epidemic and treatment advances, these changes can be readily incorporated into future analysis. And finally,

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this also does not address HIV treatment issues specific to children.

So in conclusion, we found that alternative ART rule out scenarios in South Africa left major differences in projected mortality by 2010, the benefits of ART are substantially increased with the availability of CD4 count monitoring, and two lines of therapy.

And finally, rapid scale-up of treatment can decrease the number of HIV deaths in South Africa by over 1 million by 2010.

I would like to acknowledge my co-investigators, as well as our funders, the U.S. National Institute of Allergy and Infectious Disease and the Dorister [misspelled?] Charitable Foundation. Thank you.

[Applause]

MARYLOU: Thank you, we'll take questions now. The lady with the microphone is now on this right side of the room, your right side. Does anybody have any questions?

MALE SPEAKER: Yes.

MARYLOU: Yes, [inaudible] there's somebody right behind you.

KEVIN: John, why don't you come to the front to the microphone?

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JOHN WASUNGER [misspelled?]: Thank you very much for your presentation. My name is John Wasunger from Kenya. I wondered what your modern [inaudible] looked like if you considered the TB situation in South Africa, especially in the emergence of XVI TB, and in this model is it talking it about?

MARIAN CAUPHANA: So the model we used is actually very flexible, and we have a lot of inputs and a section of our data inputs is actually the prevalence and incidents of opportunistic infections, including TB, specifically from the South African setting. So our mortality is not AIDS-related. We have mortality from background causes as well included in the analysis.

MARYLOU: John?

MALE SPEAKER: My question is about the input into the model that generated the benefit of CD4 monitoring versus clinical monitoring alone.

I think you mentioned that most of your data came from South Africa, which is appropriate for this analysis, but can you comment on that input data that generated those reductions in deaths from CD4 versus clinical monitoring.

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MARIAN CAUPHANA: So basically the way the model works is we can choose how we start our hypothetical patients on treatment. So in the case that we have CD4 monitoring, we follow that we show our South African guidelines patient start treatments when their CD4 falls under 200.

So in the model patients actually go to doctor visits regularly, and they get CD4 tests. So if you have CD4 count monitoring, then they start on ART as soon as CD4 falls below 200.

In the case that we do not have CD4 monitoring, the patients go on visits and eventually we get started on ART when they have an opportunistic infection.

MALE SPEAKER: Could I ask a question, actually one is [inaudible]. Can you explain why that it is?

MARIAN CAUPHANA: Well, we're already basically behind in getting out into antiretroviral treatments. We've got people who began, I mean, just began in 2004 and we started our analysis in 2005.

So obviously, there's been some advances since 2005, but of course we already know that there's a backlog of people getting on ART. So these people, no matter what we do, even if we do ramp up very fast, they're still going to be

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missed, they're going to die before we get to them, to those people.

MALE SPEAKER: And I guess the second question was perhaps more unfair. What do you think's going to happen; I mean what's the likelihood of each of these scenarios in real life?

MARIAN CAUPHANA: Well, I'm certainly not an expert on this. As you may have noticed, I actually subbed in for Rochelle Walensky, who probably knows a lot more about this than I do.

The rapid growth scenario is probably quite unrealistic, unless there's really some motivation and movement from international funders and people like that. But I think what I really show is how unacceptable really the zero growth scenario is, and the constant growth scenario is.

It's really unacceptable to have an increase in the average and then just because there is no increase, there's no adequate increase in the number of treatment slots to fall back, to fall behind again.

So I think that's really what we wanted to illustrate here. Like I said, we didn't address the feasibility and the costs of these scenarios and that's something that I guess

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everybody here will be thinking about over the next couple of days. Thank you, then.

[Applause]

MARYLOU: We have more questions.

MALE SPEAKER: Thank you for your great presentation. In fact, after I heard your presentation, I'm a bit scared. What is this tell of your government?

MARIAN CAUPHANA: I'm sorry?

MALE SPEAKER: The stand, the support from your government?

MARIAN CAUPHANA: I really have no knowledge of that. Again, what we're trying to do is really getting some information out and getting out there. Hopefully the government will take note; international funders will take note of what is likely to go in South Africa depending on the researches that we put in for antiretroviral treatment.

MALE SPEAKER: We're on the same sort of road, and some of this from this place can work South Africa for drug resistance testing, [inaudible] the hands of the whites. Do you have access to those facilities?

MARIAN CAUPHANA: The work we do is basically modeling. We do collaboratives in South Africa who work in treatment directly with patients and we do get data from

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these collaborators. So we do not directly have access to these facilities, but our collaborators do.

MALE SPEAKER: [Inaudible] is hazardous. You have to have some strategic plan, a way of fighting this HIV/AIDS because it is a big danger, so maybe you can't answer this alone, but you need the support for [inaudible].

MARIAN CAUPHANA: I'd like to clarify once more that we didn't - it wasn't within the scope of our analysis to address the feasibility and the cost of these things, what we really wanted to do was get the information out there to the people who can do something about this.

We are not a funding organization. We are a research group, so we're really just trying to inform people, and inform the decisions of the people who make health [inaudible] decisions, which obviously will have a great impact over the next couple of years.

MALE SPEAKER: Thank you. [Applause]

KEVIN: Okay, well, thank you very much. That was an interesting presentation.

We're sort of halfway through our program. I've been asked to make just a couple of comments. I'll do that very quickly before we actually move to the panel discussion.

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I think there were a number of issues raised, which there aren't necessarily any answers but they certainly will, they need to be discussed and they'll keep coming back.

From the Kericho presentation, the issue that came up was the starting point of therapy, clinically based versus CD4 based. Just a couple of comments about that: Clearly everybody believes and thinks that we should have much wider access and need to work towards better access to CD4 testing.

An allied question to that actually concerns, what is the right starting point? I keep being utterly perplexed that 11 years into combination antiretroviral therapy globally, we still don't have clinical trial data from when to start, and I hope we will at some stage.

Clearly in Africa, we are starting too late, certainly when we're starting clinically based, and even starting with the CD4 count of 200, when about half the patients are so mightily asymptomatic. But it's later than the median CD4 count per incident - tuberculosis, for example.

This is a huge international discussion. It's got major funding implications because if we start earlier, there's going to be many more people eligible for therapy and that's got major implications, not only for first line, but

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eventually, possibly for second-line therapy as well.

Perhaps we'll leave the issue of the differences between switching from first to second line, and substitution, which is substituting drugs for toxicity, individual drugs within a class. We perhaps could leave until we've had the panel discussion.

The issue of D4T came up, and I'm going to ask Dr. Jiltz to actually make a comment on D4T, if that's okay.

One interesting issue that came up from that Uganda presentation, a good presentation I thought, is the issue of case definitions for these toxicities.

If we are going to invest more money and resources into pharmaceutical vigilance which would clearly need to, the issue of standardized case definitions for these various toxicities is going to have to be agreed upon.

It was actually pretty impressive that, if I remember the data correctly, 70-percent of people started on that first line regimen, were still on the same three drugs at 18 months. That's actually pretty good.

We started a discussion on viral load and its utility or lack of it as a baseline measurement, and that, I think, segways into the issue of CD4 requirements or just clinical indications for therapy.

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And I just wanted to draw your attention to a session tomorrow afternoon at 2:00, Session M3, which is being held in the Serena Banquet Hall, which is a specific discussion and debate about clinical versus immunologic versus virologic monitoring of ART response. And I think that'll be an important session with, I think, some quite important new data.

And finally, Charlie, if you could get a microphone, the issue of, or otherwise just come up to the front - the issue of D4T is a troubled one. D4T, Stavudine, is no longer used in the industrialized world, or hardly at all, because of its toxicities particularly lipodystrophy, peripheral neuropathy, and so on.

WHO has given some recommendations recently to reduce the dosage from 40 to 30 milligrams. We clearly can't switch away from D4T overnight. It remains a part of the most widely used regimen.

But perhaps, Charlie, you could just say what current advice is and how you see the future, the immediate and mid-term future playing out about this.

DR. CHARLIE JILTZ: Thank you, Kevin. When the original 2003 global guidelines were issued by WHO, we were promoting a dual NRTI and an NNRTI first line, and within

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that, we were promoting what was most readily available and what was cheapest for countries to start and then massively scale up.

And the most widely available fits that combination at that time, was a Stavudine containing regimen. We included in those 2003, and then again in the revised 2006 guidelines, the standard dose cut-off for weight, so D4T40 for above 65 kilos, and D4T30 for those below 65 kilos for the adults.

Recently, we reviewed the data on this, and we had a small guideline development group meeting following the CROI meeting in Los Angeles and revised our recommendations based on some published evidence and review of the toxicity and dosing data to say as an interim that as we were expecting programs over the next few years to move away from D4T because of its toxicity, but as the interim D4T30 for all weights of adolescents and adults was a more appropriate and less toxic alternative.

And we publish this data on the Web and they are now regarded as an addendum to the treatment guidelines that we've made. And already in Malawi, which did have quite a considerable future commitments with a supplier and had considerable D4T40 purchased, has now moved to D4T30.

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And they've actually calculated there is a significant cost saving for the national program of about \$100,000, just in - sorry, \$500,000 over a year for making that small, but still significant change in overall weight of the antiretroviral that's used.

There are major implications in what the NRTI dual backbone is in first line, and I would point out there is a debate tomorrow at 16:15 in this hall, which I think I'm moderating, but I'm also talking, where we're going to discuss some of the issues around what basic first line is and then how this influences your choice in second line.

And there are clearly some countries already that are moving away to a non-Fimadine [misspelled?] analog first-line NRTI.

These will be considerably more expensive, they will certainly be less toxic, they will probably impact significantly on appearance and they may well also impact on durability and potency. We're not sure on the true efficacy, but this will have significant impacts on country program costs, if we move to a more expensive first line.

All the modeling and forecasting the countries have done has been based on the price of first-line regimens dropping.

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So there is a significant issue here about moving away entirely in D4T or in [inaudible] the alternative for it, to a non-Fimadine analog, i.e. to Nofavere [misspelled?] or Abacavir as the predominant NRTI. So if you're interested in this and some of the implications please do come to the debate tomorrow at 18:15, 6:15 here in this hall. Thank you.

[END RECORDING]