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**4<sup>th</sup> IAS Conference on HIV Pathogenesis, Treatment and  
Prevention  
Treatment of Early HIV Disease  
International AIDS Society  
and Australasian Society for HIV Medicine  
July 23, 2007**

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**ANTHONY FAUCI, M.D.:** - Tony Fauci and I have the pleasure of chairing the session this afternoon, entitled the treatment of early HIV disease. We have a number of distinguished speakers who are going to be making 15-minute presentations. Questions will be left for the end of the entire session, so that we can discuss in the context of all the speakers.

This is a particularly timely topic, as virtually all of you know, because of the continual re-evaluation of what the appropriate time to start therapy is vis-à-vis initial HIV infection up through and including evidence of deterioration in the form of sustained high levels of viremia and/or decrease in CD4 cells. And the evidence that has accumulated over the years has had us reevaluate from time to time the issue of the balance, the delicate balance between what the ultimate effective therapy, which we know is a salutary effect balanced against the cumulative toxicities of treating for a long period of time, with the weight of evidence being concerned about the level of drug-induced toxicities. Recent studies over the past couple of years, even most recently over the past year, have indicated that in fact either in the pediatric situation or in situations in which CD4 versus viremia were balanced against the criteria for starting therapy or resuming therapy and the

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indications are that we really do need to re-look at it, particularly in light of the fact that it is possible, if not likely, that some of the toxicities that were attributed to accumulative drug toxicities actually might relate to the cumulative effects of sustained viremia that have gone unchecked with therapy.

So in this context, a group was put together to discuss various aspects of that. And with no further ado, I'd like to get into the session so that we can hear from our distinguished panelists. The first in the section will be a discussion of the Recent Developments in Immunopathogenesis and the Implications for Early Treatment by Yves Levy. Dr. Levy is the chief researcher at the immunology service at the University Hospital at Henri Mondor outside of Paris. In fact, Dr. Levy is a member of ANRS and serves as the president of the scientific committee at Seed Action [misspelled?].

**YVES LEVY, M.D., Ph.D.:** Good afternoon. Thank you, Tony. So, regarding the title of my talk today, you will not be surprised to recognize some slides from my slides presented this morning by Dr. Lederman [misspelled?]. However in the next 15 minutes I will try to discuss the implication of these future pathological studies.

HIV infection is characterized by chronic and progressive depletion of CD4 T cells. However, we don't know

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yet how HIV replication research in this T cell depletion. And this mechanism is not completely and fully understood. In a recent paper published by Redrig Gasatal [misspelled?], it was shown that the correlation between the HIV viral load, which reflect HIV replication, the magnitude of HIV replication as a depletion of CD4 T cells, is statistically weak. And in a new analysis of the MAX [misspelled?] cohort, it was also, these results was confirmed. Although this new analysis, demonstrated once again that HIV viral load may account for around 50-percent of severity in the time to progression to AIDS or death.

However, another interesting point is if when we look at data for T cell depletion within HIV area in the stratum in the left four patients, for example, with viral load below 500 [inaudible], or in your right, viral load about 40,000 [inaudible] we can see that there is a large variability in the weight of CD4 T cell depletion in patients. And this indicate that viral load do not explain completely the rate of the the entire individual [inaudible] CD4 depletion in HIV infection. This raises a question: If this is progression related to other predictors, related or not directly related to viral replication, but not routinely measured in clinical practice.

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One usually suspected and discussed this morning by Dr. Lederman is chronic activation. And chronic infection by HIV is characterized by chronic activation of the immune system.

It's interesting to look at HIV models. In AGM, in African green monkeys, it's not a pathogenic of SIV infection. The rate of virus replication is as high as in [inaudible] model, pathogenic model of SIV infection in the bottom of the slide. However, these two infections, these two primates, differ that the capacity to AGM who don't develop immune activation during the chronic infection.

In HIV-infected patients, this very important study published in 1999 demonstrated that the depression of the activation marker, CD38 on CD4 and CD18 T cells, was a stronger predictor in the [inaudible] viral load of disease progression. As shown here, for patients with virus survival below six months compared to patients with survival above 18 months, we should note in this study, this study concerned very advanced patients with low CD4 cell counts, but this demonstration raised the question that HIV may lead to disease progression from mechanism apparently independent to viral replication.

An analysis of lymph node from HIV-infected patients showed also that there is a high number of effector cells in this lymph node, in that box here. These effector cells express activation markers such CD38 and these cells are

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attracted in lymph nodes as compared to lymph nodes for not HIV-infected controls. Interestingly, there is an inverse relationship between the frequency of CD38 T cells in lymph nodes and the peripheral CD4 T cell count, well, as no correlation was found in the right here with plasma viral load.

So last year's very interesting and important data showed that many things happen also in mucosal sites. Eighty-five-percent of the total lymph node tissue is located in the gut. And this has effector cells expressing CCR5 and the [inaudible] express CCR5 as compared to less than 50-percent of cells in the peripheral blood. This may explain why there is a massive and rapid depletion of CD4 T cells in the gut and this depletion is distinct from that observed in the peripheral blood. And the second point is that this depletion occurs within weeks of the primary infections and persists, of course, during the chronic phase of the infection.

We don't know the activation based on the effect of the virus or cytokines, what are the mechanism of activation during the chronic infection? However, it was proposed in the last year that this loss of CD4 T cells in the gut may be associated with the translocation of microbial products as LPS [misspelled?], as assessed here by the LPS levels in plasma. As you can see here, there is a high level of LPS in the plasma of chronic infected patients or more advanced patients.

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However, we may also suppose that there is all the mechanism, as you can see here, in acute and early infected patients. The levels of LPS is not higher than in controls. However, we know that within the first weeks of infection, there is a rapid onset of human activation.

So a very interesting question is when during the natural history of HIV infection we may detect these markers of human activated [inaudible] cohort of serum converters showed that the level of CD4 T-cells below or above 500 sets and also the level of the expression of CD17, an activation marker on CD4 T cells prior serum conversion in these subjects were strong predictors of the clinical outcome.

In another study in acute early infected subjects not treated with HAART, the demonstration of the correlation between expression of activation markers on CD4 and CD8 T cells and the level of virus replication was made. And this is a very important point because in this case, we have a correlation between the magnitude of virus replication and this expression of activation marker. However, the multivariable analysis, as you can see in the bottom of the slide, showed that the level of CD8 T cell activation was an [inaudible] predictor of the CD4 decline in the periphery, independent of viral loads.

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Therefore, the dynamic relationships within weeks of the primary infection between the host and the virus is a predictor, is a critical phenomenon that may predict the clinical outcome of patients. And this study in the AGM non-pathogenic SIV-infected models, in AGM showed that the virus replication during the primary infection is associated with the constant decline of CD4 T cells but rapid recovery of normal CD4 T cell count, and this decline is associated with a concomitant increase of expression of activation marker on CD4 and CD8 T cells.

However, in this model, it's interesting to note that this primary infection if followed by the induction of an antiinflammatory response with secretion of IL10, TGF beta and the induction of the expansion of T Regs. We and others have produced the report that HIV may drive the expansion of the T Regs during the chronic infection. And we address the same question in patients during the primary infection within the weeks after the diagnosis of primary infections. We found that T regs were detectable also at a lower frequency than in chronic infection. However, these cells suppressed in vitro the response of CD4 T cells against [inaudible] antigens but also against B24 HIV antigen.

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Whether these T regs may have an impact on the immune activation as demonstrated in SIV models is a very interesting and open question we want to address now.

Therefore in HIV infection, the primary fight against HIV, the primary battle against HIV may decide the war. So the question is how antiviral therapy may reverse this immunological catastrophe. So first, what's happened in the gut? HAART leads to rapid restoration of the CD4 T cell count in the periphery. However, the restoration in the mucosal is delayed and is variable among patients. And as you can see here, for some patients there is no restoration and for other patients it could take more than five years to look at the restoration of CD4 T cells in the mucosal sites.

The second point is despite the very well-controlled viral load and the antiviral therapy, you can see here that the level of immune activation in HIV-infected patients treated with HAART remains higher than in HIV non-infected controls. So this level of immune activation, residual immune activation, is associated with the fewer gain of CD4 T cells. Each 5-percent increase of expression of activation marker on CD8 T cells is associated with minus 35 cells and a gain and the HAART.

The other point is, what is the impact of this residual immune activation on the function of the immune system? This

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study addressed this question. It's a vaccination study on patients with high level of CD4 T cells, that were well controlled viral load under HAART and you can see here that the immune response to vaccination was predicted by the nadir [misspelled?] of CD4 T cells and not CD4 T cell count at the time of vaccination. This indicated that the past imprints the future of these patients and also that the immune deterioration of the immune system is not completely restored despite long term control of virus replication.

Another simple way to look at the immune activation in patients and to come back to simple markers in clinical practice is the evaluation of the CD4 and CD8 ratio. And in this long-term cohort of more 10,000 patients not treated with HAART, you can see here that adjusted viral loads in these patients, non-treated patients, the rate to disease progression to [inaudible] for patients with CD4 cells between 350 and 500 that were kept a low CD4-CD8 ratio is similar to that patients with lower CD4 cell counts, around 200 cells. And you can see here that the rate of disease progression for a year in these patients with CD4 above 350 is not low, is around 4- to 5-percent a year.

So what could be the implications of these results for early treatment? So first thing is the result from the [inaudible] cohort published last month in *AIDS*. I think it's

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really interesting to look at that for many patients, despite the seven years' control of viral loads, the quality – the quantity of the immuno response is not perfect. If we assume a normal CD4 cell count in non-infected individuals is around 800, you can see here that for the majority of patients, for 50-percent of patients treated with HAART at 350, these patients do not reach the goal of 800 cells. In the bottom of the slide, you can see the overall increases of CD4 T cells from medium. You can see that patients gained 136 cells during the first six months of treatment, 40 cells during the second year, and zero cells beyond three and four years. There is a plateau effect on the CD4 restoration in these patients.

So one question could be, what is the clinical implications of these low levels and the normal values of the CD4 T cells in the long term? And this collaborative study from [inaudible] Court [misspelled?] showed that evaluates the mortality rates and the mortality rates in these patients, the standardized mortality ratio is a number of observed deaths in these patients who started HAART for years compared to the expected deaths in the general population. And this ratio was calculated within each category of CD4 T cells. The first observation is if you look at patients with CD4 cells above 350, the rate of this in these patients remains high. And high, of course, are the normal of the non-HIV infected

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population. However, if we look at patients who maintain for seven years, at least six or seven years under HAART, a CD4 cell count above 500 cells, these patients had the lower rate of mortality. So these indicated that these patients, after seven years of CD4 cells above 500, reach a rate of mortality close to the general population. This reinforces the hypothesis that a high CD4 cell count sustained for years may allow patients to reach the rate of mortality of the normal, non-infected general population.

So in conclusion, we should keep in mind when we treat patients and we look at the peripheral blood research, that the concomitant restoration of the immune system is delayed in lymphoid tissues as compared to the blood. And despite a prolonged biological control under HAART, qualitative immune dysfunction is common and the quality of the restoration is predicted by the immunological status at treatment initiation. So nadir [misspelled?] of CD4 T cells and the level of human activation are predictive of the immune restoration. And it's not clear today whether the longtime control of virus replication could be sufficient to reverse this immunological deterioration. The impact of chronic activation in other conditions that AIDS events of survival is unknown.

So in my opinion, the balance between consequences of premature exposure to antiviral drugs versus a reduced

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[inaudible] benefits and increase risk of non-AIDS clinical event by deferring antiviral initiation is - remains, an open question that should be addressed in a long-term randomized clinical study.

I would like to thank friends and colleagues who have shared many of the sites I've presented today, [inaudible] for very interesting discussion, Sacha Dudenkow [misspelled?] for the gut research, [inaudible] for the [inaudible] studies and [inaudible] for cohort. Thank you for your attention.

[Applause]

**ANTHONY FAUCI, M.D.:** Thank you very much, Dr. Levy. The next speaker, the title is "Changing patterns of Morbidity and Mortality in HIV Disease," and the speaker is Dr. James Neaton, who's a professor of biostatistics in the division of biostatistics and adjunct professor infectious disease and international health for the School of Public Health at the University of Minnesota. Jim?

**JAMES NEATON, Ph.D.:** Thank you very much, Tony. It's a pleasure to be invited to give this talk. In the next few minutes, I'd like to present some data, largely from the SMART [misspelled?] study that I believe motivates further evaluation of antiretroviral treatment at CD4 cells counts higher than what guidelines currently recommend. And in particular with the focus on diseases which are currently not AIDS defining.

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This slide, which is familiar to many people here, shows the dramatic decline in the AIDS death rate following the introduction of highly active antiretroviral therapy in 1995. In the years that followed the introduction of the therapy cohorts like Cascade have enumerated the causes of death and in this cohort of serum converters prior to HAART you can see that 48-percent of the deaths were attributable to AIDS events subsequent to HAART and through recent data 28-percent of the deaths were attributable to AIDS. Likewise, if you turn it around and ask kind of the distribution of the causes of death are starting in CD4 cell counts at lower versus higher levels from the Hopps [misspelled?] cohorts among individual in the era of HAART, it started less than 200 60-percent of the deaths were AIDS, whereas starting above 200 36.8-percent of the deaths were AIDS. A higher percentage of non-AIDS mortality among people starting therapy at higher CD4 cell counts.

Now, there's many possible reasons for the changes and these causes of death. So competing risk, for example, and respect for the cascade cohort treatment was so effective in preventing AIDS people have to die of something. Potential risk factors for these other diseases, for example smoking and a large a fraction of HIV-infected individuals smoke, coinfection with hepatitis, other conditions that are risk factors for the non-AIDS mortality. Potentially, the effects

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of antiretroviral treatment itself are the effects of HIV. Whatever these non-AIDS conditions are now kind of very important from a public health as well as from a clinical point of view.

The concern about the potential effects of antiretroviral highly active therapy on as a toxicity for some of these non-AIDS conditions is largely what lead the design of the SMART trial. In SMART, over 5,000 patients were randomized, 2,752 to a strategy of biologic suppression in which therapy was used to maintain viral load as low as possible throughout the followup, [inaudible] drug conservation strategy in which antiretroviral therapy was episodically when the CD4 cell count dropped below 250, it was used. But when it came up above 350, it was stopped again. And so the notion here, the general hypothesis was by using antiretroviral therapy episodically we could maintain kind of the person at low risk for opportunistic diseases but also potentially keep them free of some of the toxicities which we thought were attributable to highly active therapy.

Well, the results of SMART, which were published last November were a bit surprising. A substantial difference in favor of the biologic suppression strategy for the primary endpoint, which was opportunistic diseases or death, a 2.6-fold increased risk of AIDS or death. But also more surprising, I

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think, was the increased risk of cardiovascular, serious cardiovascular, renal, and liver morbidity and mortality. This was identified in this trial as a supported outcome in the sense that we asked that [inaudible] oversee in this trial, not to stop the trial too early unless there was kind of consistent evidence that treatment either was beneficial for both or had thusly effected both. And you can see in this case, there was very strong evidence at the time SMART was interrupted that the interruption strategy used kind of was not working.

It's not evident from that slide, that's kind of illustrated here in what I refer to as serious non-AIDS outcomes is that when you look at the deaths that occurred in SMART, largely they were non-opportunistic disease or non-AIDS deaths. Also shown on this slide, in addition to the pre-specified cardiovascular, hepatic, and renal outcomes which as you can see were all hard, kind of clinical events if you will, MI, clinical or silent stroke, surgery for coronary artery disease, end stage renal disease and cirrhosis also added to this are non-AIDS defining malignancies except non-melanoma cancers. And you can see collectively 184 of these events occurred and the risk in the interruption group was seventy percent higher than in the viral suppression group.

If you look at the subgroups in SMART that were presented this effect of interruption or not using therapy was

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consistent among patients who came into the trial taking therapy as well as those who entered the trial not taking therapy. So for example individuals who entered SMART not taking therapy assigned to the DC group or the treatment interruption strategy didn't start until their CD4 cell counts declined below 250, whereas those in the viral suppression strategy began treatment immediately.

And you can see from this small sub-group, which is the subject of a poster at this meeting there's a striking difference, small numbers in favor of early treatment in this case, kind of immediately beginning treatment under the yes group, versus deferring it in the DC group until kind of CD4 cell counts drop below 250. The excess risk is seen both for opportunistic diseases as well as for serious non-AIDS diseases that were identified on the previous slides.

The point of this slide is to show that collectively in SMART and this is true as evidenced from many of the cohort studies, ongoing, serious non-AIDS events are much more common than what might be considered a serious AIDS event. For the purposes of SMART, these were events that excluded esophageal candidiasis and herpes simplex, otherwise all other AIDS defined events. So you can see here that there was a substantial excess risk in the DC group compared to the VS group for serious AIDS but also for serious non-AIDS. And the

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serious non-AIDS events occurred three to four times more frequently than the serious AIDS events. So a consistent story, I believe, between kind of cohorts looking at causes of death, other cohorts that have looked at morbidity that serious non-AIDS events are much more common in the era of HAART and particularly in higher CD4 cell counts.

So these findings of SMART led us to kind of do some head scratching and to initiate a series of studies and I just want to present you data from one of the biomarker kind of studies that has been conducted in the context of SMART. The general hypothesis was that HIV kind of, at the time of infection, results in inflammatory response that activates the coagulation system and that potentially antiretroviral therapy will reduce that risk. And in the absence of therapy risk is increased and the magnitude of that absolute risk is probably a function of other characteristics of the patient particularly when you think about the non-AIDS diseases that I'm talking about which are multifactorial.

One of the strengths of trials like SMART is that one can kind of biomarker studies like this within it, and so specimens were stored at baseline and during follow up the patients in both group and so that, for example, one can take advantage of the randomization and ask the question, were there changes inflammatory and, in our case, inflammatory and

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coagulation markers varied by treatment group? And also look at the clinical outcomes in SMART and carry out nested case control studies related to clinical outcomes.

In SMART, the type of nested case control design that I'm going to be presenting was that we identified cases in our case these were just patients who developed opportunistic illnesses, or cardiovascular disease or renal or liver disease during follow up. And for each case, we matched them to the control and the cases and controls were matched to have approximately the same period of follow up in the study. The cases and controls were also matched on age and gender and site at which the patients were enrolled. We randomly sampled 250 patients in the DC group and 250 patients in the VS group to count CDD at entry and among those who had one month specimens in storage as well as baseline. And in addition, concerning the nested case control component of it, we took the cases as I previously mentioned of which there were 280 patients and two controls for each case 560 matched on the factors listed on the slide.

The inflammatory and coagulation markers initially evaluated in the panel are shown here. Today I'm going to focus just on the presentation of coagulation marker D-Dymer. So D-Dymer is a fibrin degradation product that reflects ongoing activation of blood coagulation in the [inaudible]

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systems. It's a useful diagnostic tool for venous thromboembolism and it's been related to cardiovascular disease, both coronary disease, stroke, and venous thromboembolism in several large cohort studies, most recently last month in the Women's Health Initiative Trial in the United States among women showing that D-Dimer levels were associated with an increased risk of stroke.

It's been more limited studied in the HIV population. In a small group in the Swiss cohort study, it was shown that D-Dimer levels were higher in HIV positive patients than HIV negative controls. And that D-Dimer levels were reduced following the initiation of therapy. Similarly, in the kind of Wise [misspelled?] study among 144 women at different stages of HIV D-Dimer levels were directly related to the stage of HIV disease, higher levels among women with more advanced disease.

So these are the findings for the random sample of people that were chosen at baseline. This is just the cross sectional data at entry and two points of note, that overall on average the D-Dimer was .53 thirty-four percent of patients at baseline in SMART actually had D-Dimer levels which are considered above normal range. The D-Dimer were significantly higher at entry among the people who entered taking no therapy compared to those taking therapy. More importantly, kind of in terms of taking advantage of the randomized comparison, these

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are the changes in D-Dymer from baseline to one month. So you can see focusing on the underlying values that in the viral suppression group, that in the ART group, so this would be the group that came in not taking therapy and began taking the treatment in the viral suppression group, the D-Dymer levels dropped by .22. Whereas in the DC group where they stayed off therapy, there was really no change in D-Dymer levels. On the other hand, if you take the group of people that came in taking antiretroviral therapy the D-Dymer levels increased by .10 in the DC group, this was after interrupting their therapy whereas no change occurred in the VS group because they stayed on their therapy. Both of these differences were highly significant and overall D-Dymer levels increased significantly greater in the DC group compared to the VS group after one month of the trial.

The further breakdown of the group became then on therapy, divided according to whether their viral loads suppressed and you can see most of the increase – nearly all of it, of the increase that you see following the interruption of therapy in the DC group occurs among individuals with a suppressed viral load whereas little change is seen among those who entered with a viral load which was not suppressed. During this one month period in that subgroup one sees a direct relationship between the increase in D-Dymer level between baseline and one month and how fast the viral load came up

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during that one-month period. The patients for whom the viral load increased to greater than 50,000 had the greatest increase in D-Dymer.

Now turning to the case control study that was nested within SMART, these are data for 85 deaths and 170 matched controls just focusing on one of the outcomes and you can see from the colored bars that there's a rather substantial distribution in the baseline D-Dymer levels between people who died and people who survived during the 18 month follow up of SMART. Average levels were significantly different from one another and the odds ratio for being in the fourth quartile at baseline of D-Dymer compared to the first quartile was 12.4, so roughly a 12-fold increased risk of death at baseline among individuals who are in the highest quartile of D-Dymer compared to the lowest quartile.

If you further break down, adjusting for confounding factors at baseline D-Dymer levels vary by smoking status, diabetes, by kind of prior history of cardiovascular disease, by age and gender, as well as race. This is an analysis which adjusts for those factors, you can see it's largely unchanged the highest quartile versus the lowest quartile a 13-fold increased risk of death and there's a nice linear trend.

If you ask the question in terms of the change in D-Dymer levels the D-Dymer levels were measured both at baseline

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and proximal to the event of entrance. And you may recall from one of the earlier slides that a .15 microgram per milliliter difference was observed after one month between the two treatment groups. This difference in D-Dymer based upon the changes, the regression for the relationship between change in D-Dymer and these different outcomes are shown here. So that, for example, one would predict this change that we observed at one month to be associated with a 23-percent increase risk of death, a 12-percent increase of major cardiovascular disease, and a 40-percent increase risk of AIDS.

Our conclusions are based on the summaries that our group believed that data from SMART provided a strong scientific rationale for study in the effect of early treatment on mortality and serious morbidity from AIDS and non-AIDS conditions. Serious non-AIDS conditions occur three to four more times frequently than serious AIDS events at high CD4 cell counts. Treatment differences between the DC and VS are consistent among those on and off therapy and these biomarker data now provide additional evidence for the potential benefit of early treatment.

I'd like to acknowledge the many SMART patients who participated in this study, inside investigators, our cardiovascular working group who developed the biomarker study in particular Louis Cohlor [misspelled?] and Russ Tracy

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[misspelled?] and his laboratory at the clinical biochemistry research at the University of [inaudible]. And SMART was funded by the National Infectious Diseases. Thank you.

[Applause]

**ANTHONY FAUCI, M.D.:** Thank you very much, Jim. Our next speaker is Paula Munderi. The title of her presentation is, "Is Earlier Treatment in Resource-Limited Settings Feasible?" Dr. Munderi is the clinical research fellow for the Imperial College of London/Medical Research Council Program on AIDS in Uganda. Paula?

**PAULA MUNDERI, M.D.:** Thank you very much for inviting me to give this talk. I'm going to talk a little about the current practice of antiretroviral therapy in Uganda where we use the conservative initiating treatment and I'll particularly speak about some of the experiences from our research study clinic. I hope I would say that I'll be able to say what to inform our practice on when to initiate treatment. I'm hope to show that earlier treatment is feasible but also to discuss what I see as some of the potential challenges to implementing the change in treatment policy.

In my country, we use the conservative approach to treatment based on the WHO guidelines for resource limited settings. This is a page out of the 2006 revision of the guideline which acknowledges that the level that we initiate

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treatment, if we are using the CD4 count is 200. The key part of this treatment guideline is based on WHO clinical staging and the reason for this is that [inaudible] widespread access to CD4 count testing. So patients in WHO clinical stage four we are advised to treat irrespective of CD4 cell count. Patients in WHO stages clinical one and two who are not yet symptomatic we advised not treat. And patients in WHO clinical stage three, if the CD4 count is available, particularly if they have some of the clinical events that can occur at any CD4 count like tuberculosis or severe bacterial infections we should verify that with a CD4 cell count. But in general, we are allowed to treat.

After the reduction in cost of ARVs this, to me, was the single best piece of news in terms of increasing treatment access. Because what it did for us, along with this manual which is shown on the left-hand side, which is a WHO clinical staging manual, is it allowed us to initiate patients in treatment without necessarily having to wait and measure their CD4 cell count. And in my view, this is what actually allowed the treatment scale up to begin, because of the general shortage of laboratory diagnostics to measure CD4 cell counts.

And this graph is some preliminary data on the extent of treatment scale up and the cumulative number of patient receiving ART in resource limited settings. The current global

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estimates, as you all know, is that we have about 200,000,000 people now receiving therapy and the increases have happened mostly over the last three years. So really our treatment cohorts are three years old.

My country is among the 15 countries with the highest number of people treated. What I want to show here is that I think we've done amazingly well but we're still only meeting about 45-percent of the estimated national need for treatment.

And now turning back to my patient clinical population, with the conservative guideline, conservative initiation that we're using, this slide shows survival baseline CD4 in 1,000 patients enrolled in our [inaudible] clinic at the [inaudible]. Over four years of survival is about 90-percent, which is very, very good. What you see with the red line though is that in the lower CD4 strata, which is a CD4 count a treatment initiation between 0 and 49 cells there is a significant reduction in survival. However, it is still at about 82-percent at four years, 82-percent survival at four years. The patients we enrolled in this cohort all had symptomatic disease. They had WHO clinical stages two, three, or four, and all had a CD4 count below 200.

I'll go back to that slide for a minute. The other thing I wanted to point out with this data is that over a total of 87 deaths, 52 occurred within the first year and 45-percent

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of those within the first six months of treatment. Now this has also been noted by other workers who have more data. We don't have enough deaths here to really stretch this out over a long period, but that excess risk of mortality in that first few months of treatment particularly in the patients who start treatment at very low CD4 strata seems to be a feature of most treatment cohorts in developing countries.

In my view, this could be related to the fact that we are starting treatment very late in the course of the disease where there are many more opportunistic infections, quite possibly a much higher risk of immune reconstitution syndromes. But I also think that if we had better access to intensive treatment units, or more invasive, more specific diagnostic tools and more specialized treatment we could probably still improve in this outcome.

This shows the causes of death in the same cohort, in the 87 deaths that I've just shown you. As you can see, most deaths, as expected, are still due to HIV-related causes. TB is an important diagnosis at death and the HIV-related cancers, which are difficult to diagnose and very difficult to manage account for a significant proportion.

This again illustrates the limited diagnostic ability because the category that is marked as febrile events are actually mostly febrile events where there [inaudible] where a

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specific diagnosis could not be made. And we have a significant proportion where the cause of death could not be ascertained. We still ascertained the cause of death in eighty percent this.

And the overall rate of mortality per 100 person years is 2.8. It is an extremely low rate of mortality even in this advanced disease cohort. In the HIV community we're able to compare this with a pre-ART cohort where we have data on pre-ART morbidity and this rate represents a 20-fold reduction in AIDS-related deaths.

So I wanted to show this picture that this is of course to celebrate at four years into treatment some of our clinic participants when we meet we dance for joy at the fact that we're all still alive at four years.

Turning now to some of the other feasibility issues, one of the main limiting factors to me was, can we identify patients who need treatment earlier? And start treatment earlier than we are starting now? A key limitation has been the poor uptake of HIV testing or the fact that we did not have enough facilities widespread for detecting people early, counseling, and testing. Some colleagues in the teaching hospital have - as the picture shown here - have shared data on routine counseling and testing in health facilities. The picture here is in a medical ward in one of our teaching

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hospitals where fully 60-percent of the admissions, in patient admissions, are because of HIV related illnesses yet only about ten percent of these patients had ever been tested for HIV.

When this service was introduced the uptick is close to universal. We're also having expanded HIV testing in antenatal clinics because of prevention of mother to child transmission programs and they are several examples of home-based counseling also, extending testing and counseling to families and couples starting with indexed HIV-positive cases. All this has resulted in the ability to detect disease earlier, to detect disease long before our patients are due to start treatment by our CD4 criteria.

This is a small chart to show a [inaudible] cohort, the type follow up in [inaudible] and [inaudible] which I do in association with TASO [misspelled?]. TASO is the AIDS support organization and it's a community based organization that provides clinical care and psychosocial support for people with HIV. A third of these patients will have a CD4 between 250 and 350, a third will have a CD4 between 350 and 500, and about half CD4s above 500. This is just at 270 patients that we enrolled last year.

Regarding maybe starting treatment earlier, for me, the patients that I'm really concerned about are the patients in the red band. If they do not have clinical symptoms because

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the reason to initiate treatment is usually based on clinical symptoms, the CD4 count between 250 and 350, I am not sure what is best for these patients. A CD4 count above 350, however, because we're following up the patients seeing them every half a year and looking at their clinical morbidity and because we stay in touch with them I'm quite happy to reassure them, say that they do not require treatment yet and see them again in six months.

Turning again to what's happening countrywide and what's happening in the treatment programs, this just goes to show that the most frequently used first-line regimen is [inaudible] based, D43TC and nevirapine for the simple reason that this is available as a low cost generic. Uganda is no exception to this general pattern. However, going back to the consensus guidelines, which govern our national policy, there is advice that we should move to a more tolerable regimen that is non-thymidine based, that uses tenofovir or abacavir still maintaining the preferred approach of dual nucleoside reverse transcriptase inhibitor and an RTI. I agree with this particularly if you wanted to treat patients earlier because of the experiences that we've had on the medium term toxicities particularly of [inaudible]. However, if we were to do this, and in Africa we are always preoccupied with cost and drug cost, this would mean a three- to fourfold increase in drug cost. Those figures there show,

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for the current first line regimen the cost is \$121 a year. The cheapest that thymidine-based regimen could possibly become available at would be \$360 per year. And if FTC is the nucleoside the cost up to \$500 a year.

The other thing of concern is that although we do remain committed to universal access between now and the year 2012 we base our treatment estimates on figures that are generated by the UN AIDS, global AIDS epidemic. Now apparently the numbers are in need of immediate treatment according to the conservative criterion, CD4 200 and below are probably about to be revised upwards because the methodology is being revised upwards. For Uganda, what this will mean is that we have a current national need of 234,000 Ugandans needing treatment. This is about to be revised upwards to about 350,000 with enormous cost implications for the treatment programs.

So as I end, I want to note that we have observed significant benefit, clinical outcomes and survival from the conservative approach. It is possible to do research on the optimal time to initiate ART and this is indeed feasible because we [inaudible] the patients, we do have the patients, and the new data and evidence that is going to be generated needs to inform policy change. For me, the gray area is patients with no symptoms who have a CD4 350 and below. For the asymptomatic patients whose CD4 is about 350, the question

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still needs to be asked, will this reduce early mortality? Is it cost effective? However, we're still preoccupied with the balance between available resources and the extent of the disease burden.

I need to acknowledge our patients, the DOT [misspelled?] study team and these colleagues who shared data from WHO, the Uganda National AIDS Control Program and my colleagues in department of medicine.

[Applause]

**ANTHONY FAUCI, M.D.:** Thank you very much, Paula. Our next speaker is Julio Montaner. The title of his presentation is "Can We Treat Our Way out of the Epidemic?" Julio is the professor of medicine and clinical director of the British Columbia for Center Excellence in HIV/AIDS. Julio?

**JULIO MONTANER, MD.D., F.C.C.P., F.R.C.P.C.:** Thank you, Tony, before we start I would acknowledge that Richard Harrigan was originally planned to give this talk but unfortunately his flight was cancelled and he could not make alternative arrangements to be here with us today. The work that I'm going to share with you is the result of collective effort of a number of people at the BC center including much in particular of Vivienne Dias-Lima [misspelled?] who is in the audience today.

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I'm going to change gears slightly and I'm going to sort of address the topic for discussion from a totally different perspective. I would like to discuss for you some of the work that we've been doing trying to understand or better characterize what we refer to as the added preventive benefit of highly active antiretroviral therapy. And so that there is no confusion here, let me just state loud and clear that we're not talking about replacement of prevention strategies with highly active antiretroviral therapy, but rather in an environment where we can optimize prevention by the various measures that we are familiar with can we squeeze an additional preventive benefit from highly active antiretroviral therapy? That's the topic that I would like to discuss.

We believe that there is sufficient evidence out there to argue that highly active antiretroviral therapy plays a significant role in the prevention of HIV transmission. And perhaps the most compelling evidence is that I, for my transmission studies, there is a some evidence from discordant couples, there is some intriguing, interesting, and perhaps incidental evidence submerging from [inaudible] studies and I would very briefly at touch on those before I go on to some of the newer work that we have been doing over the last year.

Much of these have been summarized in the paper that we published in *The Lancet* at the time of the last international

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AIDS conference in Toronto last year. With regards to the mother-to-child transmission story, this is very well known to all of us. Since the advent of highly active antiretroviral therapy in the mid-'90s we've seen a very rapid decrease on perinatally acquired AIDS. Here you have the panels on your left hand side illustrating the USA data, very rapid decline of perinatal AIDS. The Canadian data shows exactly the same thing but it's a bit more striking in that I have data for the nominator here, the number of pregnancies that occur and you see HIV perinatally practically disappearing. So as a proof of concept this is very powerful evidence that HAART, indeed, can prevent transmission.

I'm not the first one to make that mistake. There we go. The next slide is one slide simply to illustrate the fact that now more than one cohort have documented the fact that in the presence of highly active antiretroviral therapy transmissions in the observational setting in heterosexual discordant couples have been extremely infrequent, almost nil.

The [inaudible] data, moving on the ecological data was published in 2004 in the *JID*. And what it shows it that the continued rise of the new cases in Taiwan should continue along the trail of these dashed lines and estimate in [inaudible] with highly active antiretroviral therapy was widely embraced. You see a decrease by the amounts of approximately 50-percent,

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53-percent to be precise decreasing incidence of HIV. They also used the incidence of syphilis during the observation period to argue that there has been no change in sexual behavior given that the issues of syphilis have remained steady all this time.

We were sitting on similar data around the time of the Taiwan paper. In British Columbia, we've seen a 50-percent drop in HIV new infections, no further drop since 1999 so the timeframe and the circumstances of the drop are the same. Interestingly in British Columbia, contrary to what was seen in Taiwan we are facing a very steep rise in syphilis cases particularly in the downtown core and particularly among MSM who are HIV-positive. Despite that the new syphilis, the new HIV rates remain relatively stable. As I said, the last two pieces are incidental for the most part, but I believe that all together this provides a package to suggest that highly active antiretroviral therapy is having an impact on HIV transmission in our communities.

And why is that? Well, this is data that Devania [misspelled?] has put together for us describing the frequency distribution of viral load in our patients in the treatment program in British Columbia at baseline, before they started retroviral therapy. And as you can see in the yellow they are very well clustered at over [inaudible] per mil, within six

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months of treatment you see that populationally we have shifted the median viral load to approximately 1,000 copies. And if you look at the Thomas Preen [misspelled?] data, his original studies in the year 2000 in *The New England Journal of Medicine* would suggest the likelihood of transmission going from over [inaudible] viral loads to 1,000 [inaudible] viral load in populational setting should be very meaningful.

If you look further at 24 months what you now find is that the median viral load is at less than 50 copies, once again suggesting that the effect is going to be even more impressive. So we believe that this at the bottom of the decreases in HIV transmission that we have seen in British Columbia.

We asked Vivienne to go ahead and develop for us a mathematical model aimed to correlate these two phenomena, the expansion of antiretroviral therapy that we saw between 1996 and 1999 and the change in incidence of HIV. And I'm not going to dare explain the model for you but this is what it looks like [laughter]. I hope you like it. The reason we asked him to develop this mathematical model was that we wanted to then optimize the model prospectively in the past using the data that we actually generated in the years '90 to approximately 2000. And that is illustrated here, where you see the data from the drug treatment program on the upper panel regarding

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the increased uptake of antiretroviral therapy, on the red is the real data, on the gray is the simulated data. And then the new age of infections, on the red is the BCCDC data and gray is the model once optimized to fit this data. Again we asked Vivienne to optimize the model, not because we really wanted to show you a pretty picture but because we wanted to be sure that our model was sensitive to the realities of our [inaudible] so that then we could go forward, mature the model and see what happens.

This is what happened. This is purely a gestaltic slide and you are meant not to read the details but rather to get an impression of what the lines are doing with different [inaudible]. On your left hand side you have a situation where the model uses 200 CD4 counts at the starting point for entry for viral therapy. The same parameters are maintained on the right hand side but now are using 350 CD4s. We looked at varied individual adherence, 40-percent, 40- to 80-percent, 80- to 95-percent, 95- to 100-percent. The real adherence measure on a programmatic basis in BC today is approximately eighty percent. So we're operating within this third panel on your left hand side.

We thought it was important that we explored the effect of lower adherence because if we're going to expand our coverage of antiretroviral therapy adherence might actually get

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worse if we involve people that are less willing to be treated, if you want to put it that way. Each one of the lines, 50-, 75-, 90- and 100-percent indicate that percent coverage with antiretroviral therapy for those that are eligible within that particular threshold of CD4 counts, in this case less than 200. On your right hand side, up to 350.

What you can see is a pattern emerging that is very simple whatever you do to increase antiretroviral therapy our model says that new HIV infections will drop and actually the better use of the drug, the more people you treat, the continuing slope is going to be flat. Notice that the curve on the slope is actually upwards and we could change both the magnitude of the new infections and the subsequent slope of the curve, although it's a downward curve, by improving the coverage to 100-percent. Today the coverage of antiretroviral therapy in BC, unfortunately, is only 50-percent despite the fact that our public health system covers the cost of drugs, monitoring and the likes. We believe that if we were able to expand antiretroviral therapy from the 200 CD4 to the 350 CD4s and get a reasonable adherence and a reasonable coverage somewhere in the 75- to 100-percent we would see a fairly dramatic change in new infections in the province of British Columbia.

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We have gone on to look at the affect that this would have both in the terms of the cost of HAART expansion in incremental steps from 50, which is occurring, to 75, from 75- to 90-percent, and 90- to 100-percent of those medically eligible to take treatment. And we have also looked at the quality adjusted life years gained, going from 50- to 100-percent and both results are illustrated here. The bottom line is that we wanted to be able to look at the cost effectiveness of highly active antiretroviral therapy expansion as illustrated in this slide here.

Just so that we understand, it is currently agreed that 50,000 is the threshold for a cost effective intervention in the USA. In Canada that number is usually talked about around 30,000. What this slide demonstrates is that we are operating in cost effectiveness ratios that are in the orbit of about \$3- to \$6,000 dollars, whether we consider the year 2015 or the year 2030. This means that once the added preventive value of highly active antiretroviral therapy is built into the equation the potential for this being a very highly cost effective intervention is fully realized.

I remind you that earlier today when cost effectiveness of HAART was discussed without adding these parameters the number that was tossed around was 30,000 which of course is still cost effective but what I'm trying to suggest to here is

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the fact that the added preventive benefit of highly active antiretroviral therapy in terms of relationship to transmission can totally change the scale of the potential benefit that HAART brings to our society.

Based on all these data we have proposed, and in fact we're continuing to move forward to formally test these hypotheses and what we're proposing to do is to expand highly active antiretroviral therapy with our current guidelines. In other words to re-double our outreach efforts so that we can hopefully move this so all 5,000 people who have currently been treated in our program, somewhere around seven to eight thousand in a short period of time, the hope is that within three to five years we will be able to document the change in incidence that may occur as a result of that in a prospective fashion so that these will help us to decide whether this is worthwhile idea or scheme to follow in order to assist our prevention efforts. Obviously, none of these would be acceptable under the current circumstances if it wasn't that we have a large pool of people who actually are need of treatment that are not being treated in our environment. Unfortunately this is true in our environment as it is all over the world including the developing world.

The ultimate goal of this exercise would be to construct or optimize the data that I show on this table where

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say that HAART coverage has a potential added benefit in terms of reduction of HIV transmission by which no HAART coverage associated with the 0-percent effect, 50-percent coverage, which is the current situation in our environment approximately drops HIV transmission by about a half, 50-percent. And we would like to know if what happens if we move this somewhere around closer to 100-percent of those in medical need to see whether this number moves up and based on that makes some further estimates as to how far we can push this envelope.

Obviously, this fits very nicely with the discussion on this panel here as is trying to use expansion of HAART which is undoubtedly of great benefit for our patients as a means to decrease HIV transmission.

In some circles, this thinking has been taken with a little bit of concern because of the fact that this is an untested hypothesis that brings with it concerns regarding safety, toxicity, potential individual rights. People have nightmares thinking what will happen if some governments decide to mandate HIV treatment which is something that we would not support here today or ever. There are concerns regarding resistance and I would be happy to discuss that during question period, [inaudible] epidemics, logistics, erosion of the prevention effort, potential cost, and I think all of those are worthwhile concerns that merit discussion, but

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I wanted to remind you that the way we have proposed the first step of testing this hypothesis today we are currently looking at trying to actualize changes in HIV incidents resulting from expanding HAART coverage within those in medical need, which basically makes all of those issues that you see on your left hand side listed there basically go away because these people actually meet medical criteria for treatment. They are in need of treatment and our programs have failed them by not being able to bring the treatment to these individuals. Thank you very much.

[Applause]

**ANTHONY FAUCI, M.D.:** Thank you very much, Julio. Our last speaker for the afternoon is Fred Gordin. The title of his presentation is, "Is an Early Treatment Study Important Now?" Fred is the professor of medicine at George Washington University in Washington D.C. and chief of the division of infectious diseases at the Veterans Administration Hospital in Washington.

**FRED GORDIN, M.D.:** Thank you and I'd also like to thank Jenny Hoyt [misspelled?] for organizing this symposium and inviting me to be a part of it.

This is a slide that we've all seen for many years and really set the stage for how we think about HIV and AIDS at least in the first decade of the illness. The intention,

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appropriately was on people with very advanced HIV disease because that's kind of where the action was occurring in terms of severe morbidity, mortality, and really pain and suffering for our patients. It's interesting, looking back that the middle years are titled clinical latency, and really what I want to talk about today is, is this really a period of clinical latency or is harm occurring to our patients during that period of time?

So the early research in the field and certainly most of what we as clinicians and our patients were dealing with were an overwhelming focus on opportunistic infections. And unfortunately that's still occurring in many parts of the world, as Paula said, and others are well aware of. We entered an era where this slide then became very well known of HAART as it was called in the late '90s and some still today with a marked and profound decrease in death with the availability of protease inhibitors and of course many other classes of drugs since that time.

But was we congratulated the advances we were making we became increasingly aware of the limitations of the antiretroviral therapy that we have. And while we're aware of many of these limitations what I want to focus on is the next area of concern then with the serious side effects that really were debilitating and quite difficult for patients to deal

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with. Researchers here in Australia and elsewhere in the world certainly were amongst the first to report to the disfiguring lipodystrophies that we see in people with some of the drugs. Additionally investigators in this case from the DAD [misspelled?] groups demonstrated the impact on cardiovascular events and again the fear was that the drugs were not worse than the disease but clearly were causing problems for patients and therefore we tried to balance when to start therapy versus with drugs we considered that we considered to be toxic and difficult with when do we really need to give therapy given life-threatening diseases at later stages of HIV infection. Again, some of the difficulties that we've learned from these drugs and we're dealing with through the last decade or so are their usage.

So what I want to talk about next is this really a period of clinical latency? Can we assume no harm going on to the patient event though we're not seeing some of these major opportunistic infections at the higher CD4 cell levels? The answer, of course, is no. There are numerous publications, some of which are listed here showing increased rates of cancer, increased rates of liver disease and mortality, increased rates of heart disease and mortality and, as Jim pointed out, about three-quarters of all the deaths occurring in HIV populations on therapy are in fact due to these so-

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called non-AIDS events, really asking the question, how do we define AIDS? And is it really HIV morbidity that we're seeing now across the spectrum of people's lives?

Just some data to support that. This is a slide actually that Morrow [misspelled?] showed in the 1:00 session from the DAD study again showing that all cause mortality as well liver specific mortality, I think the slide that he had also showed malignancy related mortality is not a distinct cut off at 200 or 300 cells, but really a gradient across a variety of CD4 strata.

So what has been our evolution of focus of concern? Well, certainly in the early years of HIV, most research was focused again on opportunistic infections and malignancies. We then moved into dealing with the complications of therapy itself and really at this point a lot of attention on the serious non-AIDS morbidities is something that we need to deal with in terms of, where do we go next? So I think rather than looking at this as a latent period, we really need to look at this as a long period of ongoing morbidity from HIV infection. Which begs the question, can we do anything about this? Can we help the patient through this period without causing undue harm?

There's some intriguing data from cohorts again, actually Morrow showed a portion of this slide earlier. I'll

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[inaudible] appreciate lending me this slide looking at the UK CHIP and CASCADE data [misspelled?]. And if you look outside the yellow box at the bottom is who we're treating now. And so again for people naïve with CD4 cells between 200 and 350 the rate of AIDS or death is approximately five per 100 patient years. But it is not small within the box, and again, a grading in the white going up 2.5, 1.6, 1.0. Substantial morbidity, mortality in regions that the guidelines in most places – really, all places – would say don't treat, meaning above 350.

Interestingly, if you look at the green bars next to it, which are patients on therapy, the rates again decrease. Now, this is not a randomized control trial but it gives a hint that at each CD4 strata people on therapy are doing therapy are doing better than people off therapy. The right column of CASCADE is similar and I won't walk through it.

This is a slide Jim showed earlier. This is a group within SMART who were either totally naïve or off therapy for six months of entry. So this becomes a randomized when to start trial, albeit a small one. VS group then would be people on immediate therapy, the DC group are people being deferred until they reach 250. So this is probably really only the randomized when to start data that's out there. Jim walked through the slides so I won't go through it again but the

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yellow box looks at again the serious non-AIDS events. So to focus on that people on the VS group, people on therapy two events occurred, at a rate of .5. People off therapy until they met 250 cells, 12 events occurred at a rate of 3.9 statistically significant. I don't think enough to change any guidelines but certainly intriguing that treating at higher CD4 cells may impact the serious non-AIDS events.

So what are the guidelines? Everybody knows them well. They vary in the United States and most developed nations it stays treat between 200 and 350, but it's really not a very strong statement right now. Basically it says treatment should be offered with considerations and pros and cons. The WHO also uses the word consideration to treat between 2 and 350 and unfortunately as Paula's recognized many national guidelines and limited resource settings say, please only treat under 200.

So I think we need to look a new paradigm. We need to look at should we be looking at the treatment of the broader spectrum of HIV disease not just patients with opportunistic infections and late stage infection.

So the question would earlier ART prevent morbidity and mortality in HIV infection? Well, there's parallels in other diseases. None of us would accept lipid values of cholesterols of 240 any more, systolic blood pressures of 160. So we've recognized in other diseases that more aggressive or earlier

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treatment can be life saving. Again, it begs the question, should this be the case with HIV infection as well? What will it take to change guidelines? To change clinical management? I think clearly we need to demonstrate that early HIV infection has an impact on both serious AIDS and non-AIDS events. We also need to balance all of these other factors, what would the cost be, as Julio just walked through very nicely? What would the cost effectiveness be? Getting data that could be used by various locations and nationalities to create guidelines appropriated for their location. What about all of the problems with the drugs? The problems have not all gone away, although many of the drugs are now easier to take and safer but again it would need to be a balance between reducing the serious non-AIDS events as well as AIDS against the costs and problems associated with the medications.

One of the questions that's come up is can we find the answer from cohorts? And just recently this month Inside [inaudible] co-sponsored a workshop on this in the Washington area. Bruno Letterberger [misspelled?] from Switzerland put this data together and allowed me to use it. He surveyed 93 cohorts in the world, essentially all the cohorts doing HIV work. Shockingly, 90 responded. So I guess people who do cohorts don't mind filling out surveys. Interestingly, 25-percent of the cohorts going on right now have no information

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at all about non-AIDS conditions and 36-percent of the remaining, about a third of the remaining cohorts only have free text, meaning it's not a standardized way of capturing the data. The data collection he felt was very heterogeneous and end points were only review for less than 30-percent of the cohorts. So I think clinically trials are needed. Cohorts have many biases. Jim could to speak to this and many of you in the audience better than myself. They provide unbelievably important information but I don't think can answer this question.

Randomized clinical trials on the other hand can rigorously examine the associations that we see and really test interventions to see again as people across the spectrum of this afternoon's talks have pointed out.

Well, are there trials going on? There are. So right now, and there may be more I apologize if I did not catch them all. There are studies here in light looking at children, one of which share, I believe will be presented as a late-breaker and recently had some DSMB interruption of some of the patients. These are pediatric studies of small numbers looking at infants and children with advanced HIV disease. There are two studies going on in adults. One in Haiti looking at patients who are being randomized to be treated between 200 and 350 or wait until under 200, again in an advanced population.

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And then ACTG5245 pairing with the HPTM, discordant couple study, asking the question whether or not in discordant couples half of whom are being treated at entry between 350 and 500, half between 200 and 250, what's the clinical impact as well as the rate of transmission impact? Now, these studies, all of which are going on in more advanced disease appropriately are using endpoints of survival, failure, first-line therapy, opportunistic infections, WHO stage four disease, tuberculosis, events which occur at late stage disease. They do not, however, other than one as a secondary endpoint look at non-AIDS conditions. So getting back to this paradigm, I believe we need a study to really examine when at higher CD4s treatment should be initiated.

One such study is the Insight Network Start Trial, this is study which is under design, soon to begin will look at HIV infected patients at entry with over 500 CD4 cells, half of whom will be in an early immediate arm, meaning treat over 500. And the other half in a deferred arm treat at 350. The initial estimates at sample size for a run in phase pilot is approximately 1200 and for a definitive trial approximately 3000. The endpoints for this study will be serious AIDS as well as serious non-AIDS. That is major heart disease, MIs, strokes, renal failure requiring dialysis, cirrhosis, et cetera, as well as death from any cause.

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I think on all of these studies based on Yves' work and others', many, many others, it's going to be critically important, Jim just showed today the value of saving samples for further underlying hemo pathogenesis work. I think nested sub-studies looking at these areas of adherence, resistance, immunology, neurocognitive function, things that are of critical importance to patients and their lives as well as to providers in terms of being able to make good decisions on what to do.

So Jenny [misspelled?] and others asked me to address should we be doing an early treatment study? Is this the time? I think clearly we can do the study now. We have the drugs that are potent, they're durable, they're more readily available. The drugs are clearly less toxic and easier to take than in the past. We've got a research infrastructure available in both resource rich and resource-limited settings and we've demonstrated the ability in SMART and many other studies to do high quality long-term follow-up in HIV work.

Should a study be done now? I think there's compelling evidence that the morbidity in early HIV disease is quite substantial, again up to three-quarters or more of all the events are these quote non-AIDS illnesses. There would be millions, literally millions of people identified with HIV infection from new testing and counseling efforts over the next

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decade. Many of them will have low CD4 cells and we already know they need treatment. Many, many others will have high CD4 cells and we need to know what to do with those patients. So there's really an urgent need to get definitive evidence to inform guidelines to make clinical decisions. I think it's almost understatement to say that the evidence would have profound global impact.

So Dr. Fauci and I are both from the Washington area, and there was a football coach named George Allen, this is American football of course. And we were used to many losing seasons in Washington and his motto was, "The future is now." We can't wait anymore to be good in the future. We need to do it now. So I'll just end by saying I do think the time is now for this study. Thank you.

[Applause]

**ANTHONY FAUCI, M.D.:** Thank you very much, Fred. We'll now open the session for questions. If you have questions if you could find - there you go. Mark.

**MARK HARRINGTON [misspelled?]:** This is Mark Harrington from Treatment Action Group. This is unusual but I'm going to ask a question to the facilitator. Ten years ago on March 13<sup>th</sup>, 1997, which was two weeks after the conclusion of the ACDG 320 trial, which was one of the last major clinical end point studies in people with under 200, David Barr [misspelled?] and

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I walked into your office in Bethesda and asked you to fund a study of when to start. And you told us it was the most important question, and now we're meeting 10 years later with this incredible scale-up. Are you willing now to fund such a study?

**ANTHONY FAUCI, M.D.:** [Laughter] I was willing then. The study was not proposed. I'm willing now of course. In fact Fred just mentioned the study that he was referring to with Insight that's actually going to be the first step towards that. So the answer to your question Mark, in your usual fashion, is yes, we are willing. Next question.

**JOE ERON [misspelled?]:** Hi, Joe Eron from Chapel Hill. I just have a couple of questions for Fred. One is a clarification. HP10052 is a 1,700 couple study and it also intends to look at both AIDS defining events, death, and serious non-AIDS conditions much as you outlined for the Insight study. My question is the current guidelines aren't really actually based on randomized control trials either and it seems to me you've presented very compelling information from cohort data and from the SMART study that I think would actually argue very strongly that we should actually change our guidelines and treat patients with CD4s greater than 350. Our current guidelines now aren't based on a randomized trial, so I

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wonder whether you might want to comment. It was a pretty compelling presentation for just starting above 350.

**FRED GORDIN, M.D.:** I apologize if I got the ACTG trial numbers wrong.

**JOE ERON:** HPTN. HPTN052. It's not an ACTG study.

**FRED GORDIN, M.D.:** Right, I was talking there about the ACTG portion of it. But again I may have had that wrong. I had actually recently rotated off the guidelines committee myself. There are people in this room, including the chair of the committee, who may or may not want to speak really more directly to that. I guess my feeling is I think the evidence is intriguing but not compelling enough to make a decision to say, for example treat at 500. I think treating at 350 as opposed to where it now says 200 to 350, I personally think there's probably enough evidence to move it up to be a stronger statement than it says now. That letting people drift down to 200 is too low. I don't think there's enough evidence this is myself personally to say start above 350 at this point.

**ANTHONY FAUCI, M.D.:** Other questions?

**BO LYNN [misspelled?]:** Bo Lynn, Los Angeles. If the data safety monitoring board felt strongly enough to stop the SMART trial and a lot of the compelling evidence that you presented for doing a start trial comes from the SMART study I guess I would kind of push Joe Eron's question a little bit

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further and say is it really ethical to do a start study now?  
And why isn't more compelling to you than you state?

**FRED GORDIN, M.D.:** So the SMART study, again, allowed patients to go to 250 and as I said a minute ago. I now think based on that and much other information I personally think probably that's too low. This study would allow patients to go to 350 and again would be starting naïve patients above 500. So it's a different population and it was also different set points.

**ANTHONY FAUCI, M.D.:** Next question.

**JEN SVOGEN [misspelled?]:** Jen Svogen, Copenhagen.  
When I hear the last two presentations I hear Fred Gordin arguing for the individual patient to start on therapy that there's a potential to improve this person's prognosis. When I hear Julio Montaner argue, he's arguing that this person will not transmit virus so that's not a benefit to the person itself, but rather to the society around him. I would be curious to hear, Julio, how would you accept to provide treatment early on if it does not provide benefit to the individual patient who's receiving it? And put it a little bit more sort of direct way, how much benefit would there be to the individual patient before you can see that it is justified for the added benefit? This is, of course, not for your current

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discussion in patients who are in need, but rather if you push the envelope upwards. Thank you.

**JULIO MONTANA:** Thank you Jen. So let me be very clear. At the present time we're not advocating to treat outside of the current guidelines which would be as high as 350 for the reasons that you have had heard. I think that the matter of whether, if and when we have evidence to confirm that everything that I showed is true within the current treatment guidelines I think a clinical trial would be needed to properly understand the role of earlier treatment. But I think that at the same time the way antiretroviral therapy is moving, that perhaps that trial will never happen depending on the answers that Fred's study can provide us. I view these things evolving in synergy. One caveat though, and I think this is what you need to just put it on the table, we've been for too long pretending that the guidelines reflect the reality and as [inaudible] showed at [inaudible] the reality is that people have been untreated even in areas where the treatment is really available as in my own backyard. I think that we collectively need to make a commitment that expansion of the guidelines is very important but it should not distract from our effort to achieve one hundred percent coverage of those that are in medical need based on the current guidelines because if today we're having only fractional impact in those populations it may

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be very easy and convenient to distract our resources to treat people at the earlier stage of the disease but at the end of the day we first need to do what is important which is to treat those that [inaudible] today.

**MALE SPEAKER:** Julio in one of your slides where you showed that a fifty percent expansion of HAART led to a fifty percent decrease in transmission and then the one hundred expansion of HAART you had question mark, would that be essentially one hundred percent decrease in transmission. Since your HAART expansion is based on current guidelines which are not early treatment that we're trying ask, which is the question of this session would you assume then that if you did, and it's going to be difficult to get one hundred percent expansion of HAART and you still did not get to nearly one hundred percent that the transmissions would be among those people who are not advanced enough to fall within the guidelines but that who would in fact add that extra percent. Is that going to be your assumption?

**JULIO MONTANER, MD.D., F.C.C.P., F.R.C.P.C.:** Right. Let me say, then, I suspect that our 50-percent is a very bad number because it's been generated with observational data, collected retro respectively and that we don't really know how many confounders are playing there. So I put it out there just as a teaser, if you want. If you want my own expectation is

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that there would be, if we increased the number of people in treatment from say to 5,000 to the 7,500 we probably will see from 50-percent to a 75-percent decrease and there would be some sort of proportionality there.

Having said that, there are two things that are of concern. The rates of transmission may not be equal, the natural history of HIV as you probably know. And the second there are recalcitrant transmitters, behaviorally speaking, who may not be easy for us to reach. In other words, they have the hard to reach populations and all of that may come into the question. This effort needs to characterize who those people are so we get a better understanding how much we can push antiretroviral therapy to help them derive a benefit.

**ANTHONY FAUCI, M.D.:** We have a question here and then we'll go there.

**HANS FILHAGER [misspelled?]:** Hans Filhager from Munich. If the basis of our earlier treatment would be immune activation could we imagine other things than just triple therapy as being influential on immune activation? Say corticosteroids? There is some anecdotal data that it may do the job between 500 and 350 or there are other medications that you can think about or just HAART? There should be options probably?

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**ANTHONY FAUCI, M.D.:** Who wants to handle that question? You did the pathogenesis part, Yves, so go ahead.

**YVES LEVY, M.D., Ph.D.:** I think it's a good questions, the place of immunosuppressant [inaudible] for example however today we don't have any evidence for that. I think we are discussing something that can change [inaudible], so we have small data and a clinical trial on cyclosporin, for example. The PI was Michael Edema [misspelled?] there is no clear beneficial effect on CD4 cells. We are discussing something in the long term with endpoint on non-AIDS related event or AIDS related events. I think perhaps there was some [inaudible] pathological question around immunosuppressive drugs but we don't have evidence to date that this may help to maintain life CD4 cell counts in the long term.

**HANS FILHAGER:** There is some anecdotal evidence with corticosteroids in that area. It's published.

**YVES LEVY, M.D., Ph.D.:** But it's anecdotal.

**HANS FILHAGER:** It is anecdotal, sure.

**ANTHONY FAUCI, M.D.:** On this side here.

**CHARLIE GUILLS [misspelled?]:** Charlie Guills from World Health Organization in Geneva, where I'm responsible for writing and coordinating the treatment guideline process. I have a comment just to reflect on a couple of the points Paula was making around the challenges in Africa at the moment about

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trying to do treatment scale-up when the first point is that the burden of disease is going to go up fifty percent with better estimation of treatment need. And that is to the conservative guidelines for WHO. So the 7,000,000 people in need of treatment is going to go up to nine, maybe 10 million people in need of treatment. The second point is that as we move towards more tolerable regimens the prices of those regimens is going to go up three to fourfold. And I wonder in this sort of circumstance we are playing enormous catch up, particularly in Africa to try to get people on treatment, the relevance of considering a treatment trial around CD4 or 500. And I have a particular question to those who are looking at this and considering this in terms of the non-AIDS disease and how critical is that on the background mortality and causes of death in the community? Bearing in mind that in most African high burden countries the epidemiological transition has not yet happened.

And I wonder and I worry that all the non-AIDS disease is very relevant in industrialized countries, but it doesn't really make that much difference in Africa. I'm really concerned ultimately that we're going to get it into a situation where we're going to have two different guidelines, one for the industrialized north and one for the poor south. Up to now we've been able to finesse it so that we do have one

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WHO set of guidelines which is universally applicable. But I fear the way this is going particularly if we do have clear evidence from the north to start at 500 this won't be so evident in the south.

[Applause]

**ANTHONY FAUCI, M.D.:** It's a good point. Here and then back.

**CHIRSITINA MOSINI [misspelled?]:** Christina Mosini, Italy. The guidelines on starting treatment were based on analysis by statistician. As clinician we were very happy to move on to 350 because below 200 was really too risky. And almost nobody of us was treating patient with such a low number of CD4 unless they were AIDS presenters or late presenter, which still a presenter, almost half of our population that start treatment every year. Don't you think to prevent a very low number of non-AIDS event like myocardial infarction or liver disease or kidney disease you will expose patients with a low rate of progression with a CD4 higher 500? So some of them will be long-term non-progression to the development of side effects very rare now like osteopenia, or not known. I mean they talk about 10 years to see lipoatrophy. Don't you think that the risk is too high now to perform such a study? We don't know the side effects of most of the side effects of the most of the drugs we are using now.

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**JAMES NEATON, Ph.D.:** I can address it in part, perhaps, and then maybe others. The clinicians may want to say something but I think as you move potentially the treatment guidelines up the issue you raised about risk benefit becomes incredibly important. And so I don't think it should be done unless you firmly establish in the right kind of studies that the benefits outweigh the risk. I think kind of the data suggests now from the cohorts, from SMART, from a number of sources, that there's a potential for benefit. The potential for benefit is rather substantial in terms of these non-AIDS diseases. Whether that benefit is realized and outweighs the risk can only be determined in a properly designed study.

**MALE SPEAKER:** [Inaudible]. Two additional comments. The first one on the SMART study, it clearly it's an [inaudible] issue for the [inaudible] community [inaudible] will participate to such a study in the next few months. My second comment is for the countries from [inaudible] and most patient are now and a large proportion of patient that do not reach CD4 cell count higher than the 500 for example. So we have a [inaudible] patient about one sort of patient with CD4 cell counts lower than 500 or 350. The question is what we have to do with this patient with immuno constitution which is the [inaudible] during a long period and we have to think about on such a clinical trial.

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**ANTHONY FAUCI, M.D.:** I was just told that technically we have to be out of here very soon [laughter]. I don't know why but we have to be out of here. I'm not so sure there's another session. So why don't we just take two more questions? I'm sorry for cutting people off because a higher authority than I has just sent me a note. Why don't go for a question there and then a question here?

**MALE SPEAKER:** [Inaudible] just in response to the [inaudible] presentation from the WHO, we're always caught half way in between being part of the developing world but I have a part of the country that's more affluent. And in my clinic, we sit with about 2,000 patients on treatment. We have 12,000 files. What happens is these patients come in for an HIV test, come back for a CD4 count, it's above 200 and they're told to come back in six months for a repeat CD4 count and there's a huge loss to follow-up in these patients that do not qualify for treatment at the initial stage. If one would move it up even to 350, which is quite acceptable at this stage, one would catch a huge amount of that patient that we lose now, our loss to follow up in our patients that have gone to treatment below 200 is exceptional, response is exceptional. But our losses to follow-up is in the patients that do not qualify for treatments initially.

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**ANTHONY FAUCI, M.D.:** Are you inferring then that if we increase it up to beyond 350, we would even lose less people to follow up because we would have treatment for them. For example, if the 500 study showed that it's best to start at 500 that you capture. Sure.

**MALE SPEAKER:** For us, we would like to move up to 350 but would have added benefits.

**ANTHONY FAUCI, M.D.:** Next question.

**JONATHON ANDERSON [misspelled?]:** Jonathan Anderson from Melbourne. I guess I just want to comment on what you might be using in studies when you try to think about the burden of disease for people who might have CD4s between 350 and 500. Rather than base it purely on something in terms of quantifying non-HIV diseases, non-HIV direct diseases, I think you really need to make the primary focus the quality of life outcomes. And as someone who has a mild interest in all of this kind of health economic stuff, I reckon that's part of the problem that you need to make sure that the study is going to stand up when you come back to your third-party provider, your funders and your governments and that's the most important thing. Because what my patients care about as a primary care physician is their quality of life and what government's care about is spending money to maintain that quality of life. And so I'd argue you'd need to think about that first. Usually

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it's just tacked on the end as a quality of life because someone said we should. I'd like to see that as a primary outcome measuring your study if it's really going to mean anything.

**MALE SPEAKER:** It's not unreasonable. I agree with you and I think a fundamental part of the study and early treatment needs to be in assessment of quality of life and as Fred indicated cost effectiveness. That needs to be coupled with the clinical outcomes that we possess.

**ANTHONY FAUCI, M.D.:** Thank you and I'd like to thank the speakers for their presentations and the audience for their participation.

[END RECORDING]