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**When and What to Start as First-Line Therapy?  
PEPFAR; the Global Fund to Fight AIDS, Tuberculosis and  
Malaria; UNAIDS; UNICEF; the World Bank and the World  
Health Organization  
June 4, 2008**

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**PETER MUTENYA:** Thank you. So ladies and gentlemen, we are coming to the breakout session to discuss a very important topic, a very critical topic. I am our moderator for this session, my name is Peter Mutenya [misspelled?] from [inaudible] Center here in Kampala. I have got some distinguished speakers who will give us some insight into this very important topic.

At the end, we hope you will participate with the questions or ideas of your own and please do keep your questions, perhaps you write them down so that we could tackle them at the end.

To start us off is Dr. Elliot Raizes from CDC and he will be giving us a talk, a comparison of the adult national antiretrovirals guidelines of 15 PEPFAR focused countries. Dr. Raizes?

**ELLIOTT RAIZES, MD:** Okay. Yes. Thank you to the organizers of the meeting for allowing me to be part of this distinguished panel and in 2002, as part of the three-by-five initiative, WHO published recommendations by fore scaling up ART by using a public health approach. These guidelines were revised in 2003.

In 2005, WHO, in anticipation of further revisions, queried 39 countries to determine concordance with the 2003 WHO

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ART guidelines. Their findings were published by Beck et al in 2006 in AIDS. The study found that most countries had to develop national guidelines and concordance was high regarding criteria for starting ART, lab investigations, and choice of first line but not choice of second line therapy - excuse me - not choice of second line therapy.

The most recent WHO Guidelines were published in 2006. Among the changes noted are that Stavudine is no longer a preferred drug for first line regimens. Zidovudine, Tenofovir, Abacavir, and 3TC are now first line options and in addition to 3TC and treatment options for patients with hepatitis B co-infection are now addressed.

The PEPFAR Adult Treatment Technical Working Group realized that the degree of implementation and incorporation into national ART guidelines in PEPFAR-focused countries was unknown. Therefore, the most recent guidelines for ART in adults from all 15 PEPFAR-focused countries were obtained and reviewed.

While we relied on written documents for our information in response to our requests, six of the PEPFAR country teams validated the information described in this presentation.

Information collected from the 15 sets of guidelines included data publication, criteria for starting ART,

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recommended first line regimens and dosing, criteria for switching due to toxicity or failure, recommended second line regimens, and regimens for hepatitis B co-infection.

Half of the focus countries have not published updated guidelines since the 2006 WHO update. Although one country disseminated a manual last year that probably functions as a de facto update.

Criteria for starting ART was reviewed. In concordance with the WHO 2006 Guidelines, there is agreement among all the countries that patients with stage IV disease should all be starting on ARTs. For patients with stage III disease, 11 of the countries also require a CD4 count of less than 350 before starting ARTs.

Differences among the countries were also detected regarding initiation of ART for stage I and II disease with most countries still delaying therapy until the counts fall below the 200 to 250 range. Countries do use clinical staging alone when CD4 counts are not available.

This next slide is just to review with you the summary of the first line ART regimens as recommended in the 2006 WHO Guidelines. I am sure most of you have seen this graphic before.

So in the 15 countries, in addition to 3TC, the preferred NRTI in the first line regimen is Zidovudine

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[misspelled?] in five countries, AZT in six, and D4T or AZT in one and Tenofovir in three of the PEPFAR-focused countries. All the countries whose guidelines were published after the 2006 update now recommend either Zidovudine or Tenofovir based regimens.

In 2007, WHO recommended reducing the dose of Stavudine for adults greater than 60 kilograms from 40 milligrams to 30 milligrams twice daily. This was based on data suggesting a decreased toxicity with equivalent efficacy. Guidelines that were published since then all reflect that recommendation. Two-thirds of the countries continue to list Nevirapine as the NNRTI of choice in first line regimens but one-third do prefer Effervesce.

Eight of the countries specifically require WHO grade III or IV toxicity before substituting alternate first line antiretrovirals. For the other seven countries, the guidelines do not specify standardized criteria for substitution.

Treatment failure criteria - all the countries have adopted the WHO clinical criteria for treatment failure. That is development of a new or recurrent OI after six months, recurrent after six months or stage IV disease - development of stage IV disease.

As a reminder, the 2006 WHO criteria for immunologic failure is either a fall of the CD4 count to pre-therapy

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baseline or below, a 50-percent fall from the highest level recorded for the patient, or a CD4 count level that stays below 100.

Most of the guidelines recommended the use of immunologic criteria to determine treatment failure whenever possible specifically when CD4 counts were available. Nine countries used the WHO criteria for immunologic failure. Five countries actually uses CD4 count drop of only 30-percent from peak to define treatment failure and one country defines immunologic failure as any decline in CD4 count on two consecutive samples.

Ten countries specified recommending viral load testing when available for virologic failure. While the WHO definition of treatment failure is a viral load of greater than 10,000, there was a wide range of definitions among the countries. When a patient satisfies the definition of clinical or immunologic failure, five of the countries also recommended virologic confirmation at least when viral load testing was available.

Second line therapy - in line with the 2006 WHO Guidelines, the most commonly recommended second line regimen, as seen in the guidelines of nine of the countries, is Abacavir, dianacine [misspelled?] and a boosted protease inhibitor usually, lopinavir or ritonavir. About half of the

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guidelines also mentioned Tenofovir as an option in the second line regimens.

WHO recommends a first line regimen containing tenofovir and FTC or 3TC in patients co-infected with hepatitis B. This is the preferred regimen in the five countries whose guidelines specify treatment for hepatitis B co-infection but the others did not specify any treatment for hepatitis C co-infection.

So in conclusion, most countries continue to recommend the delay of initiation of ART and asymptomatic HIV-infected individuals until the CD4 count falls below 200 to 250. The 2006 WHO Guidelines state that one should quote - consider treatment at 200 to 350 cells and initiate before the CD4 count drops below 200 cells.

Since publication of the 2006 WHO Guidelines, eight countries have revised their treatment recommendations. Preferred first line regimens now include AZT or tenofovir, the dose of Stavudine has been reduced to 30 milligrams twice daily and second line regimens are now consistent with WHO Guidelines in those countries. For six of the remaining seven countries, first line regimens continue to include Stavudine.

PEPFAR focused countries published guidelines are consistent with temporary WHO Guidelines. However, half of these guidelines have not been updated since the 2006 WHO

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Guidelines update. Like the earlier published Beck study, this study fails to categorize the implementation of these guidelines at the facility level.

Countries are encouraged to update their guidelines on a regular basis. Creating addendums or brief updates may be a more efficient process than the multiple meetings and revisions that typically are required. PEPFAR should be able to assist in the dissemination of these updates in a timely manner.

Countries should be encouraged to formally evaluate the level of compliance with their national guidelines among implementers. This will aid in assessing programmatic quality, formulating cost projections, and in the forecasting of ARV-related commodity needs. I want to conclude by thanking all of the folks in the PEPFAR world who helped me gather these guidelines. Thank you [applause].

**PETER MUTENYA:** Thank you very much Dr. Raizes for that presentation that has brought us up to speed with what is happening in the PEPFAR countries. For the next presentation, there is a slight change. Dr. Ndwapi of Botswana is not with us but we are happy to introduce Jim Shepard from Botswana to give us the next presentation, which is the policy, cost, and programmatic implementation of changing the CD4 cutoff at 350. Dr. Shepard, please?

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**JIM SHEPARD:** Good afternoon. Thank you Chairman. I have to apologize for Dr. Ndwapi. As some of you may know, there has been a recent change entirely democratically and well organized in the President of Botswana but it also resulted in a reorganization of a number of the ministries in Botswana and the ability of Dr. Ndwapi as a director of the MASA program, which is a national antiretroviral program, to attend - was compromised at the last moment and so I have been asked to stand in for him but I am afraid I do not have a presentation. So I am going to summarize some issues associated with raising the CD4 threshold for initiating therapy with particular reference to Botswana.

I should also add that I am with the CDC Botswana but I have been there for three and a half months. So I guess in the kingdom of the blind, the one-eyed man is king so I happen to be up here talking to you.

I was actually on the recent guidelines committee in Nigeria as in my former position with the University of Maryland Action Program and we decided that clinically it was the evidence was growing that earlier initiation of antiretroviral therapy was clearly indicated and that waiting for people to develop greater immunosuppression had long-term consequences and I am sure you are all familiar with the number of studies that have come out recently to show that.

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So in Nigeria, we decided in the guidelines committee that if the physician or the provider and the patient were in agreement that ARTs should be started then 350 was an appropriate cutoff regardless of the clinical situation that the patient found themselves in.

I have to say that these deliberations were entirely clinical. There was no consideration given to cost. There was no policy or health economist on the guidelines panel. We were nearly all clinicians and it did not seem to make a huge amount of difference anyway considering that Nigeria still had a long way to go to initiate all the people that would qualify under the more stringent guidelines. So we did not feel as though the decision we were making would have immediate economic consequences.

However, in Botswana, actually the situation is quite different. In fact, Botswana has just issued its 2008 guidelines, the updated version. The hardcopies have gone out to all the site and the take home points for our discussion are that Botswana has raised the CD4 threshold for initiating therapy to 250 - CD4 count of 250 from 200, where it was before, principally because of the widespread use of Nevirapine and the concern.

There was a potential hepatotoxicity in those with CD4 counts - women with CD4 counts of 250 to 350 on Nevirapine and

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they have changed the first line recommendation, which was Stavudine to Tenofovir plus Nivivadine [misspelled?] plus an NNRTI and there in the process of running down drug stores of Stavudine throughout the national program and pushing through stocks of Tenofovir to replace it for new patients and for people on Stavudine. So they intend to switch people from their first line regimen of zidovudine analog and at leads stavudine to Tenofovir.

The interesting thing about Botswana's program for other African countries is that they have gone further down the road that most sub-Saharan African countries have started upon. So their program, which began in 2001, has reached almost 100-percent coverage of all those that qualify for antiretroviral therapy. They have about 95,000 people on ART throughout the national program and this is estimated to be somewhere between 90 and 95-percent of those of 290,000 HIV-positive people in Botswana that would qualify for therapy.

So they have got where many others in other countries are trying to get to but what the immediate consequences of raising a CD4 threshold from just 200 to 250 is estimated to mean in terms of the program and the cost and I cannot give you a dollar figure but I leave that to you to estimate - is approximately another 20,000 people immediately qualifying for first line antiretroviral therapy.

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That is an enormous bolus of humanity entering a system that is still in what I would call chronic emergency mode. So in 2001 and subsequently they developed a national network of treatment care sites like many other African countries - certainly Nigeria, which I have experienced firsthand in relatively temporary facilities to handle the influx of chronic care clients that the system required and at this point, Botswana's national program is saturated.

New patients that qualify for antiretroviral therapy have long waiting times before they can get their first prescription. They are seen in extremely crowded adjunct sort of semi-permanent metal huts. They are quite nice huts but they are huts nevertheless to one side of the original district hospitals, say where the care is given and so they have begun to explore what is called a public/private partnership in an attempt to refer patients that are currently on antiretroviral therapy to less acute care settings for continuation of care.

Now the immediate result of qualifying 20,000 more patients for antiretroviral therapy remains to be seen in terms of these policies. There will have to be very widespread referral of stable patients out of the more technically able and laboratory sites so that the new patients that qualify for antiretroviral therapy can be seen in those places and it is a

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process that essentially has to happen immediately according to the national guidelines.

The committee of the guidelines also seriously considered raising the CD4 count to 350, which we estimate would immediately qualify 50,000 people. So half as many people again for first line antiretroviral therapy and I think that the policy costs and programmatic issues associated with that immediate rise in the number of patients that will qualify for therapy inhibited them somewhat to pick 250 as the cutoff.

So I hope that that has been helpful for the general discussion and I have not misrepresented the National Program of Botswana, which indeed is a very impressive effort that has reached almost all of Botswana that qualify for therapy and we will have some significant challenges to reach those new Botswana that have immediately qualified for antiretroviral therapy as a result of the change in the CD4 cutoff. Thank you [applause].

**PETER MUTENYA:** Thank you Dr. Shepard for that presentation. Another slight change in the program, we will now move on to Albert Mwango the Zambia Minister of Health and then Charlie Gilks from WHO will come at the end. Dr. Mwango?

**ALBERT MWANGO, MD:** Good afternoon everybody. I am going to give an overview of the rollout of tenofovir in Zambia. My presentation will be as follows. I will give a brief background

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of Zambia and the epidemic. I will look at the scale-up of the ARV program and also look at the new ART protocols, which we have put in place and follow through with the steps that have been taken in the rollout of tenofovir within the country and then based on this, we look at some of the lessons that we have taken from the process.

Zambia is a landlocked country with nine provinces divided into 72 districts. It has a population of about 12 million people with HIV prevalence, based on the 2002 demographic and health survey, at 15.6-percent but recently the new survey has shown that it is now at 14.3-percent.

We have approximately 1.3 million Zambians living with HIV and with this background, the government of Zambia initiated an ARV program within the public sector. This role started with domestic funds and as now, been supported with global funds - PEPFAR, Unit AIDS and Clinton Foundation funding. The disease burden parity stands at 352,000 people requiring ARVs.

This table basically shows the scale-up of the program since it was initiated in 2003 to date. We started with - in the first year, 143 patients, who were started at two pilot sites. We are currently looking at 170,000 patients receiving ARVs. The red line shows the actual need that you had in the country over the years. In the last year, we have had

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challenges of human resource and this has been hindering the bridging of the gap that we have to reach the actual need. Currently, all these 170,000 patients on treatment are accessing services from 315 sites around the country.

This is a scale-up for pediatric ART. In terms of activities started at the end of 2005 and since then we scaled up dramatically and right now, we are at around 44.2-percent access based on the estimated burden in children.

We switched the first line from what was already described in previous presentation from AZT D4T [misspelled?] based regimens to tenofovir-based regimen. This is currently now our first line and this was introduced in 2006 in June although the rollout of this new regimen started mid-last year.

This is how our current regimens look like, first line and second line. Some of the important reasons why we had to make this change are highlighted on this slide. Based on proven potency of TDF [misspelled?], more favorable mutation pathways in the regimen that we are currently using now - the advantage with this is that we have preservation of future options of patients in case there is treatment failure on the first line. Also with the new regimen, we have once a day dosing, fixed dose combinations available.

This brings about [inaudible] burden and improved or better adherence. Also there is less intensive laboratory

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demands on the new regimens and there is also fewer side effects such as peripheral neuropathy, lipodystrophy, and anemia with the new regimens. Initially we used to have a high incidence of substitution and full switching due to the D4T toxicity. So these are some of the primary reasons for moving away from the old regimens.

Some of the cardinal steps, which have been taken in the rollout as follows - there are basically five important things that we had to go through. They may appear to be serial but there were times when we had to move back and forth to constantly date [misspelled?] on each of these items. I will go into some detail on each of the items.

The process for policy change, we discovered, was a very challenging situation because there is not that part to take when we want policy to be changed. So some of the things we will go through, which we found to be very important, are information gathering. People who make policy change need a lot of information and we also used pilot programs where we had introduced enough of our, as a first line just to have more information on how it can be implemented in Zambia.

We reviewed information using many facets including getting input from internal and external institutions - institutions like Johns Hopkins, IHB in the U.S. We also looked at clinical efficacy and safety of the new regimens. We looked

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at financial implications and also around the number of scenarios of how best we can introduce the new regimens. As you know, these drugs are most costlier than the older regimens.

We looked at supply chains in terms of where we are going to get the products and what lead times we had to the new products. As you know, every country is now striving to get the new regimens. So this has got implications on supply. One of the most important pieces is really getting advocacy from all stakeholders. We have to sell the idea. We have to sell solutions and strategies to different stakeholders.

Then there was the process of developing the guidelines. We first released a first draft of the guidelines and that was at a time when we had the issues of virus of being withdrawn. This had shaken some of the confidence of patients and other stakeholders in ARVs. So we were sending our drugs, which were abandoning old regimens with this back draft but we, nonetheless, went ahead and we got feedback and we improved on the guidelines. There were issues about kidney function assessment and this was an important feedback. The feedback was incorporated into the guidelines and the final release was made.

Another issue that needed to be looked at was really the health systems that would be supporting the new regimens. So for practicality sake, we had to review the systems such as

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laboratory capacity to do creatinine clearance. We had to look at the training packages, the refresher courses and also had to look at our logistic management systems, which was responsible for quantification procurement and forecasting of the new regimens.

We also had to review clinical practice. There were things, which were neglected such as height - determining creatinine clearance. We calculated creatinine clearance. So these are issues, which we went into and looked at as a whole. Based on this, we made recommendations.

There also had to be administrative preparedness introducing new guidelines, required that the supportive structures were ready to support the change. We had to have authorizing memos. Back home, this is very important.

Before any sublevels below a national level take action, they need to have the permanent secretary authorize changes such as policy change. We had to give technical [inaudible] to management at Ministry of Health. We had planning meetings with prevention health officers on the intended change of the protocols.

There were technical briefings with partners implementing partners, academia, the UN system, funding agencies, and treatment literacy groups. We also had to set up orientation for providers who were currently providing ARVs in

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our facilities. We managed to accomplish this in a short period of time where also into the two districts and the nine provinces we covered and this was by March 2007.

An important aspect of any new policy is basically to monitor its effects and evaluate its outcomes. A number of things we needed to look at such as patient response, although this is more going to be done with the full evaluation that has been planned. We also had to look at the prices. The prices of the new regimens are quite high. So we have to be on the constant lookout for opportunities that are low in prices and also look at our stocks just in case we run out or we have [inaudible] outs and then there were transition challenges meaning changing patients from the old regimens to the new regimens. This had to be looked at very closely.

One of the transitional challenges is in how we were having uptake of the new regimens. Currently 161 sites are rolling out the new regimens out of the 315 ART sites. This represents about 25,000 patients on the new regimens and in March 2008, we had dispensed about 27,946 patient months. That is in that one month only.

What we did not anticipate was the popularity of this regimen. The number that we are looking at in March 2008 is doubled what we had anticipated. So right now, we are looking

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at a situation where our quantification was - had to be changed upwards.

This came about because there were stable patients who were supposed to continue on the old regimens but after having heard that there is a newer and better regimen, patients demanded that they change. So this is something that was not anticipated but this is what we have observed.

For the other older regimens, they are still going up and this has been due to a number of reasons. Basically some sites have not yet switched because they do not have capacity to do creatinine clearance estimates and in some situations, there are patients who are switching from the D4T - 40 milligram regimens to the 30 milligrams. So we have seen that the trying on 30 is still rising.

We also have been looking at, on the trends, 40 milligrams doubled in based regimens and fortunately, this is going as anticipated. We are actually decreasing on phasing out this particular regimen. Looking at our estimates, by April 2009, we will have phased out completely D4T - 40 milligrams regimen.

Monitoring the prices - this was one of the most difficult situations that we had to encounter in that - the cost of treatment per patient per year was going to rise and in this case, from as low as 200-percent to 350-percent, we are

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still looking out at the cost prices. Currently the new regimen are ranging at \$343 U.S. dollars to \$430 although prices are going down. So this cost will probably be going down in the months to come.

Patient response, currently we have positive and as I said, overwhelming response to the newer regimens and we have not had any serious adverse responses being reported to date. A post-implementation evaluation is being planned to do a more thorough investigation of how patients are actually doing on the new regimen.

This has meant, basically what we have learned is that you need a functional element, which has worked and this is an essential component in switching over to the new regimen. The process of changing protocols - we found that the approach that we had is one of the best approaches that we have had in Zambia when following up policy change.

This exercise gives us an opportunity to spring clean our guidelines. Basically getting those things that are new and beneficial to patients and get out all those little items that we found to be hindering good progress on treatment. An important component also that we learned from the process was that feedback can make your protocols more robust and more acceptable.

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Also the transitional changes that are highlighted to have been quite instrumental in improving the way that services are being delivered in terms of improving clinical practice. Looking at the prices, we have seen that the more that you put patients on the new protocols; the prices will keep coming down. The more countries that will also join in this will find that [inaudible] will be more affordable and much more accessible.

We have also noticed that a continued monitoring of these activities are very important because then you do not run out of drugs and you keep patients on treatment.

These are the new protocols that we have that we are using in Zambia. You can find them on the [www.zambiahivguide.org](http://www.zambiahivguide.org). The process has involved many collaborators, implementation partners, and this is a well less than exhaustive list of people who have participated in the process.

It has been a very good experience for Zambia and it has given a lot of morale to the team that is working on rolling out the new protocols. Thank you very much [applause].

**PETER MUTENYA:** Thank you Dr. Mwango for that presentation. Now following is Ishmael Katjitae, Minister of Health and Social Services in Namibia. He is going to be talking to us when and what starts the view from Namibia.

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**ISHMAEL KATJITAE:** Good afternoon. I will actually thank the previous speaker for making my job so easy especially that they mentioned almost all the issues, which I actually wanted to mention. I am supposed to talk about when to start and what to start on.

First of all, let me discuss just two words, which I want to bring up is that Namibia is a large country around about the size of the - the combined size of Kenya and Botswana together. It is scarcely populated with a total population of two million.

Now let me take you through the outline of my presentation. I will take you through Namibia's silent HIV epidemic. The first line regimen and the challenges and the way forward. Since 1992 up to 2006, we have actually been conducting a national HIV prevalence in pregnant women on a bi-annual basis and as you can see, since in 1992, we started off with a prevalence rate of 4.2-percent. It picked up in 2002 at the prevalence of 22-percent but it went down to 19.9-percent in 2006.

We look at the estimated number of HIV positive people in Namibia since the onset of this epidemic. We are currently having 212,000 people living with HIV/AIDS in Namibia. The number of patients on HAART in the public sector from the time when we started off - we started off in June 2003 up to March

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2008, are around about 48,000 but one must take into consideration that there are still about 20,000 patients in the public sector who are still not included in that number.

Let us look at the Namibia criteria for studying HAART in adults. In 2003, we started our rollout program starting off with a WHO stage IV and a CD4 concentration of less than 200. We have recently revised these guidelines and we have now moved on to starting our patients on a WHO stage III or stage IV. The CD4 threshold for the general population has actually remained the same. It is less than 200 and for pregnant women, it is lesser than 250.

The criteria for studying [inaudible] infants and children have actually been like this. It is for the WHO - anyone presently with WHO stage IV disease, all of them actually treated and those with stage III disease, they are actually treated if they are younger than 18 months and those who are older than 18 months are treated according to their CD4 count and their clinical status especially depending on their - as to whether their co-TB or their other conditions, which are mentioned there.

The main focus is actually to first try to stabilize the presenting opportunistic infections before one starts treatment and for stage II and stage I disease, that is also a CD4-guided decision.

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Now let us look at the adult first line regimen. Our previous regimen included D4T, 3C, Nevirapine, but obviously in line with the recommendation regarding the D4T toxicity, which changed to AZT, 3TC, and Nevirapine but it is obviously also not always possible to use that regimen. So there are also other alternatives, which you can actually see and there again Stavudine is actually officially in these regimens.

What we have actually recommended in this situation is actually that to start everyone on the dose of three - 30 milligrams twice a day regardless of their weight. And what we also further on doing is for the ones who have got to stay on Stavudine, we are only allowing them to stay on for a period of not longer than 24 months.

Now there are two major comorbidities, which have also influenced our decision on our first line regimens and they are tuberculosis and hepatitis B virus comorbidities. These conditions are actually - there is a high prevalence of these conditions and these were TB - we are among the countries with the highest case loadification rate of 700 plus of 100,000.

So obviously we had to come up with something and in that case for TB, we are using AZT, 3TC, and Effervesce and again, we are faced with the dilemma of sometimes having pregnant women presenting with that condition as well and in that case, we are using AZT, 3TC, and Effervesce if the patient

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presents beyond the first trimester and most who are presenting in the first trimester, in cases where we cannot, we are considering using a [inaudible] new regimen, which includes AZT, 3TC, Abacavir,

Obviously generally in the first trimester and then we switch over to the AZT, 3TC in the [inaudible]. And for hepatitis B virus IV infections - we have actually noted that with our patients and ARV programs that there is a prevalence of between 12 and 14-percent HIV coinfection in these patients and for that reason, we actually for quite a long while, we have actually been using Tenofovir, 3TC, and Nevirapine if patient is asymptomatic and the ALT is lesser than three times the normal. Otherwise, we use [inaudible] instead of Nevirapine for the same type of regimen.

Now the first line pediatric [inaudible] in Namibia, what we are using is actually - we were in the process of actually considering continuing with AZT, 3TC and Nevirapine but because of the fixed dose combination, which was actually presented to us at the time by the Clinton Foundation, we decided to backtrack and use Stavudine, Lamovidine [misspelled?], and Nevirapine.

The benefit being that actually it is a once daily dosing and also the problem of actually syrups, which can be very cumbersome and also the problem of compliance with these

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big amounts as well. That is where we actually decided to come on Stavudine and the fixed dose of Stavudine and Lamivudine and Nevirapine but obviously now that we have actually released our guidelines, we have realized that there are indeed a fixed dose combination for AZT, 3TC, and Nevirapine. So we would have to reconsider our decision and consider to go back on our initial thought of actually using AZT, 3TC, and Nevirapine.

The challenges are towards these challenges and the main challenge is actually that we all realize that a CD4 count of lesser than 200 at initiation is actually too low and our technical advisory committee are considering to raise the CD4 threshold to lesser than 350 at initiation for better outcomes on treatment but obviously that brings out its own challenges as what was actually previously mentioned on the previous presentation.

What ART is actually putting those where advances is first on treatment, you may find a patient with a CD4 count of 50 compared to a patient with a CD4 count of 300. Those two patients are not in the same category very often. Most of the time, the one with the higher CD4 count will actually be looking very well compared to the one with the CD4 count of lesser than 100 and starting the one.

I mean all these patients are actually lining up and they are cueing up for the same type of treatment and if one

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[inaudible] to start the one with the better clinical condition, you may actually end up with a big political outcry where people are likely saying that this is actually favoritism and as such, that was actually the advice which we actually received from our politicians not to consider that but nevertheless we are in the process of doing that.

At the same time, the cost will also be increasing on the ARV program because more people will actually - will have to be accommodated and the problem - we do have a problem with human resources and also the infrastructures will - you hear about it on the previous presenters that we are talking about crowded ARV centers.

And this is actually what we will have to take into consideration and at the same time also, patients who are starting off at the higher CD4 threshold, might not be as sick as the ones with the lower CD4 count, might not be very reluctant to comply with their ARVs and that itself may actually pose a problem of future resistance in future regimens and second line regimens. So all of this has got to be considered.

Another messy caveat, which we have actually experienced with AZT is actually the problem of Namibia. We actually, from my clinical practice, have actually been seeing patients on a monthly basis who are presenting with HVs

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[misspelled?] or between two and three. And it is not always that these patients are actually lucky to be picked up very early.

Some of them actually end up dying and those who are lucky enough to present early enough have got to receive multiple drug - blood transfusions, and we have also noted in some of those patients that they are actually - that they will - that they do not even respond to repeated blood transfusions and they will, on the longer run, have to be given very expensive recombinant [inaudible] and this is also not sustainable. It is really for our systems.

So that brings us back to consider the choice of our first line regimens. In this situation, we are considering using Tenofovir in the first line for the one reason that the combination of Tenofovir and FTC [inaudible] is actually cheaper than AZT and 3TC and it is also available. It has actually been available in the private sector - in our private sector for a long time.

The combination of FTC and Tenofovir and Effervesce is also a good option because it comes off as a once daily dose pill, in terms of compliance and the convenience of its dosing and that it was also previously mentioned that using Tenofovir in the first line preserves AZT and D4T for use in the second line if Tenofovir-resistant only [inaudible] 65 are mutations

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can develop and so one can actually move into using either AZT or D4T and but the other way around is not possible because failure on AZT or D4T leads to development of multiple times limited treatment options for NNRTI classes. Abacavir in the first line for us is actually not an option yet because it is very expensive. Thank you [applause].

**PETER MUTENYA:** Thank you. So we now come to our last presentation by Professor Charlie Gilks of the WHO and he will be talking to us about implications for guidelines, cost and implementation for adult and pediatrics. Charlie Gilks.

**CHARLIE GILKS:** Thank you very much Peter and good afternoon ladies and gentlemen. It is usually a problem being the last presenter at the end of a very busy day but I am pleased to say that you are all awake and I think that is a testament into the excellent presentations that have preceded this talk. So thank you for all staying awake and actually even staying in the room.

Now I have been given the task to talk about this and I am going to try and talk about adults, pregnant women, and children around some of the issues of when to start and what to use and I think it follows on very well from all the previous talks but permit me, before I get into the meat of the presentation, just to start with this slide.

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These are the figures for progress in ART scale-up globally in low and middle-income countries that were announced and formally released on June the second, on Monday this week, and I think as you all know, the world's best kept secret - that we hit three million people on treatment just around the end of 2007.

So while we did not make three by five, I think you will all agree that we have achieved three by seven and I think it is important to reflect on that, jesting aside, to consider what has enabled low and middle-income countries to sustain and indeed slightly increase the pace of ART scale-up because nearly a million patients were newly started in 2007 when at or around the time of 2002-2003 when PEPFAR was starting out and committing billions of dollars to this, there were many skeptics who said this was not going to be possible.

I think and I would like to believe that the global guidelines that have been referred to have - the WHO have produced through all the experts and there are many people in the room who have contributed to that expert process, has contributed enormously to that as part of the public health approach to ART.

I think it is important just to emphasize here that we have tried and on the slide you can see the three current guidelines is the harmonized approach. We have adults and

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adolescents on the left in yellow. In the middle, we have treatment and for pregnant women and it is very important to consider these women as a subset - those who require treatment ideally harmonized with what nonpregnant women and adult men and adolescents require.

And, of course, ARV prophylaxis of those who do not require treatment and in finally, pediatrics because we promote family therapy and for supply chain management, it is much easier to have a small number of products that cover the range and it is much easier for people and the decentralized clinics who are dealing with adults and children at the same time to try, by and large, to use the same products.

Now to support those, we do have this very important document, which is the clinical staging of HIV for adults and for children, which also came out in 2006, the revised guidelines. I think it is just important to dwell that all the previous presenters have discussed CD4 as the main marker but in fact, for the majority we believe, of people newly starting treatment, they are still being assessed and enrolled clinically without CD4 counting.

What is important here is to note that for the adults, which is the middle panel and the children on the right, is that we adopt and promote a four-clinical stage process both for adults and children and prior to the 2006 revisions, there

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was for some reason, there was a three-stage process for children and a four-stage process for adults. So again, in terms of training multipotent staff at the lowest level, this sort of harmonization is very important.

We have also harmonized our immunological classification across all ages and this is actually - this table does come from the pediatric, the dark blue treatment guidelines - 2006 guidelines and you will note here that above the age of five years, we consider a young child immunologically equivalent to an adult and we have here severe immunodeficiency classified as a CD4 of less than 200 or a CD4 percent of 15 but that is not on this slide because this is just the CD4 counts for that column.

So again here, a harmonized process to try and represent the needs of infants, children, adolescents, and adults as part of our general and overall process.

When to start for adults - this is our current recommendation and several of the previous speakers have referred to it and here we mix clinical staging and CD4 testing if it is available and although I have not got a slide for it, it is important to note that within this there is a little footnote, which does refer to the particular needs and differences of pregnant women and we recommend pregnant women, if they are symptomatic with stage III or IV disease, and they

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have a CD4 less than 350 then they should automatically start on treatment.

But to some extent, these treatment guidelines and recommendations are regarded, as many of the speakers have previously alluded to, as relatively conservative. Although in fact, we have not done very much validation for those patients who are in clinical stage III and for whom we recommend everybody should be treated. How many of those actually do have really quite high CD4 counts because they have opportunistic infections like tuberculosis or bacterial infections, which are quite common in the community.

A few data from Malawi suggests that, in fact, there are quite a few people with high CD4 counts who are presenting with stage III who are therefore starting earlier than the CD4 - 350 cutoff would make.

This is a slide that is relatively new and I must recognize Siobhan Crowley in the audience here who works in Geneva in WHO who has very recently formed an expert group to revitalize the infant recommendations, which the colleague from the Namibia showed earlier.

These are the new recommendations and the block in yellow is to point out that following the share recommend - study - the randomized trial of early births - it deferred treatment in infancy carried out in South Africa and which

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actually still has not yet been published but nevertheless, we have managed to stay in front of the information process here by getting these recommendations out before the peer-reviewed publications. So I think we have done quite well in terms of speed here.

To note - that we are now recommending any infant should start treatment before the age of a year, infancy being defined as a child within the first 11 months of year before their first birthday - that every single infant, when they are diagnosed in infancy, should immediately start antiretroviral therapy.

That, of course, brings in other challenges, which I am not going to talk about today about infant diagnosing using HIV, DNA, or RNA PCR. This is a radical departure, which will have significant cost implications and clearly programmatic rollout implications.

So then just a few issues around when to start and I am first of all, going to start with what about some of the issues with current guidelines and I think the first thing to discuss is the access to technology for measuring CD4 counts or the health system processes for getting those results back in a timely fashion to the patients and the treatment center, recognizing that the two are actually often quite different in that you may have a machine that is there and working but it

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may be the result does not get back in time to influence clinical decision making in an appropriate way that is useful for your patient.

One of the issues here is getting the decentralized CD4-based strategy that all the previous speaker have been referring to out into health center and to district hospitals where continued scale-up towards universal access is predicated upon. We have to reach out to the lower level healthcare facilities to really be able to achieve universal access. How do we mix this and marry this with a CD4-based strategy?

We also need to think of the challenges for children where it is a CD4 percent rather than an absolute count that is necessary and the technology for measuring CD4 percent is much more complicated currently, although we believe there be some new developments soon to make it easier.

The second issue is maintaining the pace of treatment scale-up and the capacity issues to enroll more patients or the financial constraints that many programs actually have in meeting the existing country targets within the national guidelines, which are through with the conservative current WHO recommendations.

In many countries, there is a treatment slot in each of the treatment centers and this is often filled before the need and the demand for treatment is achieved and there are also

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places where there are treatment [inaudible] slots that are there and allocated but they do not have sufficient human capacity to enroll patients who, everybody agrees, are in need of treatment.

The third point, and this is a really critical point that I suspect many in the audience are not aware of is that recently, the spectrum process for countries to calculate their disease burden, the inputs into the spectrum program have been changed, as a result of the alpha network and the recognition that survival with prevalent HIV infection is actually longer than had been assumed and it is a three-year survival now reckoned to be from - when median survival from when an individual achieves the conservative time for an adult or adolescent to require treatment, CD4 - 200 or stage III and IV.

That has, using the new evidence that it is a three-year rather than a two-year calculation, spectrum is going to show that for every country that uses it that the treatment burden is likely to go up by about 30-percent just using current guidelines.

The fourth point to recognize is that within the current guidelines that we have for PMTCT, there is incredibly limited initiation of treatment for maternal disease rather than for prophylaxis in almost all PMTCT programs.

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Malawi is one country that reports that and instead of about 20-percent of enrollments in to national programs that should come from PMTCT centers, the last quarterly report was about 3.9-percent woefully inadequately ability to deal with what even is in the current guidelines.

What about shifting it to an earlier initiation of 350 as clearly countries are considering? I would point out that all the data that - that there are no randomized trials out there, which is why this is a controversial area, which it insights a lot of excitement and interest. We had to extrapolate from cohort data that it may be more appropriate to start at a CD4 count of 350.

But I do have to caution you that almost all that cohort data has come from cohorts in industrialized countries or high and middle-income countries where background mortality rates are very different from what the background mortality rates are in low-middle income and low income countries.

So I do not necessarily think that a direct extrapolation from cohort data in the north is so useful here and we do urgently need new data and I am not sure actually we can afford to wait for the results of randomized trials here because we need to make these policy recommendations globally and nationally very quickly.

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The cost and feasibility of moving to a 200 to 350 CD4 cutoff, we have already heard a couple of country estimates that this is likely to increase by 30-percent, 20 to 30-percent more eligibility. This is on top of, please remember, the additional 30-percent of increased disease burden by the increased life expectancy.

So countries can expect to increase their disease burden if they go into a 350 cutoff by about 50-percent and I will caution again the issue here that when we are reporting globally and nationally on coverage against the denominator that is those in need of treatment that if you change to a 350 threshold.

And if you also include the new spectrum, you will see immediately your coverage figures dropping by 50-percent and this will be catastrophically undermining unless there is very careful preparation of the president, the Prime Minister, the Minister of Health, and of course the press. It may be more appropriate to start to think about moving over towards reporting numbers on treatment, which is in fact, how the U.S. does it. It is never attempted in the U.S. to report coverage of treatment need.

Finally, if you do move to a recommendation of 350, what about Nevirapine as the cornerstone for the majority of people who are newly starting treatment? Our current surveys of

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countries reckon there is about 60-percent of newly started people in low and middle income countries are using Nevirapine based regimens and Nevirapine is contraindicated in women with CD4 counts above 250.

This is going to be a problem but I must emphasize that - and none of the previous speakers mentioned it - there may be a major prevention benefit from moving towards an earlier initiation of therapy.

We have limited data on it but it is clear that the more people you treat successfully and reduce their viral load to below detectable or very low, this may have a significant impact of the population level on HIV transmission and again we need data on this urgently.

Finally some of the issues around some of the discussions that have been had - not in so far in this session but about the idea to offer universal combination ART to all pregnant women and to extend this to all women who are breastfeeding if the national policy is to continue to support breastfeeding in PMTCT programs rather than moving to formula feeding.

Now, what is not discussed, at the moment, is whether one should stop or not once you have initiated combination ART and here I think the data from the SMART study are relatively

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compelling to suggest that once you start ART, at least in the north, you should never stop it.

So if countries are embarking upon this or thinking about it as a component of a PMTCT program, they do need to recognize this may be locking every single woman who has been pregnant and started ART then into therapy for life.

Is it feasible in antenatal settings to actually implement this? Remember that what is considered a very simple, if suboptimal, intervention single dose Nevirapine, is still by itself woefully underutilized in centers - PMTCT centers where even testing and counseling has been rolled out.

So I am not sure that the idea that combination ART is going to be a simple intervention is actually going to make up for the shortfall in the system's delivery that are bedeviling PMTCT programs.

Of course, we also have the use of what to use for all women if they are going to have universal treatment for pregnant women with a caveat about Nevirapine. Some countries are considering boosted protease inhibitors for pregnant women but I will remind you that the cornerstone of current treatment policy in every country is to reserve boosted protease inhibitors for second line therapy. So are you going to then prematurely initiate boosted protease inhibitors second line therapy for all pregnant women?

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There is a triple nuke option. I know triple nukes particularly for many people from North America are regarded as suboptimal and subefficacious but there may well be a role for this as the colleague from Namibia suggested earlier.

Finally, what will this do for our harmonized and uniformed recommendations that we tried so hard in 2004 to 2006 to bring together? Is it equitable to have a totally different treatment recommendation starting for a woman according to her pregnancy status and I am not sure that we have really thought about the equity issues here.

Quickly now just to think about what to use - this is the updated slide that we used to illustrate the 2006 recommendations to note on the left what is used and recommended for first line and on the right, what is recommended for second line, and to note that Abacavir and Tenofovir, the non-thiamine analogs are actually in between.

We did not just recommend them for first line. We recommended countries could consider using them for first line or that they could continue to use them in second line. So there is a bit of a dilemma because if you move to Tenofovir first line, what do you need to use for second line?

This is the table for infants and I think it is important to note here under - in the bottom two lines, which is what should be used for infants under the age of a year,

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bearing in mind our change recommendations for initiating ART as soon as infection is identified and diagnosed in an infant under the age of one year.

The consensus view of the experts was actually to use boosted protease inhibitor for this rather than the triple nuke alternative, which some people were promoting. The difficulty with this is the lack of availability of products and the really quite challenging issues of using liquid formulations, which is the only product that is available at the moment for boosted Lopinovir for low infants and there is no licensed preparation for infants less than six kilos of the boosted protease inhibitor. So we do have challenges with our new recommendations for infants.

I want to talk about this just to think then about some of the issues that previous speakers have dwelt upon and the three issues are the continued use of D4T and we have heard actually rarely to be alarmingly how some countries are continuing to recommend and purchase D4T40 despite having been at least two years of recommendations not to use this and just to use D4T30. Some of the issues around moving over to the non-thiamine analogs, Tenofovir or Abacavir first line and particularly the advantage, at least in some circumstances of one pill once a day.

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None of the previous speakers who have discussed Tenofovir have pointed out one problem with it is that there is an age restriction on using this and that because of bone mineralization problems, we cannot recommend Tenofovir for children and it is, I think, it is less than 15 or less than 16 years of age. So this does not fit well with harmonized recommendations that include young adolescents and children and that is likely to be a problem for some countries. Abacavir has a much better profile and is indeed widely - if more widely available now and there is a scored fixed dose combination with 3TC that is available in the pediatric formulation.

Although previous speakers have said with some certainty about all the data on toxicity for some of these products and particularly D4T, I will remind you that in fact, almost all the data on D4T40 is from industrialized countries and we have very limited data on toxicity of D4T in general in frequent programs including PEPFAR programs that have rolled it out and we have no data on whether D4T30 substantially reduces toxicity sufficient to make it still recommendable in some countries if cost is a major issue.

We are sure that Abacavir hypersensitivity is much less important in Africa, much less prevalent because of the low prevalence of B5701 HLA phenotype.

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There is a major problem around the need to do renal screening prior to the initiation of Tenofovir. I gather Zambia has actually had to purchase biochemistry analyzers for all the sites and I think it has got up to about 160 in total but that does produce an extra health system cost and it is not just the cost of the machinery. It is the availability of laboratory technologists in all these sites to be able to do these tests and do them in volume.

One other - that we discussed - previous speakers have discussed the cost issue but I will say that if countries are facing an issue around the move to starting at an earlier threshold or even just trying to recognize the larger treatment burden that will exist with the new spectrum calculations in their countries, that reduces the cost component.

There is also the issue of the cost component if there is going to be a move towards non-thiamine analogs first line. So all the recommendations we are talking about have significant cost implications and if you put the two together, you are looking at four to five times cost increase if one is to go to universal access.

So in conclusion - I am sorry if I have gone a little bit over time, globally guideline development is challenging, very challenging. Unlike PEPFAR, we cannot just focus on 15 countries. We do have to have recommendations and guidelines

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that really do try and recognize the needs of very diverse countries.

And we do also have a major balance to try and keep it between being very permissive in the guidelines, trying to drive the ART agenda forward with less toxic, more durable and perhaps, more potent regimens with the reality that we need to maintain these guidelines as relevant to most countries because if they are irrelevant then countries will disregard them and we will not move in the current guidelines and I do think we have to have some focus on equity of access across all of those in need.

If we move towards much more expensive first line regimens in an earlier start, we may end up benefiting only those people who can access the clinics and the centers where this is more widely available and fall into that typical development track that all the developments' benefit is congregation, a few numbers of families and communities that much better access to certain services be it education, health, or agricultural outreach.

I think finally, the process - one of the issues is also is the timeliness of this. We heard that eight of the PEPFAR countries have not actually even aligned their national recommendations in line with the 2006 WHO recommendations. So we also have to think about the time it takes and we heard very

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eloquently from Zambia of what the process is involved, in fact, to change national guidelines even around just one domain, which is a single treatment change.

So changing and upgrading guidelines is a major undertaking for us at globally in WHO and of course, it is a major undertaking in countries.

Finally, just to point out that we are moving now towards, in WHO, an updated process for developing guideline recommendations, which is based on the great system, which tends to promote randomized trials as opposed to cohort or observational data. It tends to promote hard clinical endpoints rather than surrogate markers.

And, of course, with HIV that is moving away from viral load or CD4 immunological surrogates to harder clinical endpoints of clinical disease, age-defining disease, and death, and within our new processes, we are focusing as well on costs and cost effectiveness, feasibility at the country level, and issues around the toxicity and tolerance and patient and client user perspectives. Thank you [applause].

**PETER MUTENYA:** Thank you Charlie for that presentation, which has got some of the discussion presented by other colleagues bringing us to your time - the audience. I think the way we go about it is to have a series of questions, some of them tend to interact so to overlap and then we will have them

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answered by the panel. So please questions or comments are now welcome. Yes?

**MARTHA BATUNU:** Hello. My name is Martha Batunu [misspelled?] from WHO Ethiopia. My question is for the Zambia presentation. It was my initial [inaudible] during your presentation that you said the setup of your based the regimen gets - popular, it has become very popular and you ended up having more patients demanding for it and you said to reach people who are already on old regimens to attend a [inaudible] regimen.

So my question is what is the recommendation on your guideline about switching people who are - who have been on D4T-based regimens to Tenofovir-based regimen. Thank you.

**PETER MUTENYA:** Okay. Let us take a second one from you.

**JOHN WASANGA:** I thank all the presenters. My name is John Wasanga [misspelled?] from Kenya. I wish to direct my question to the Zambian presenter [inaudible] about your regimens in children because you seemed to have talked [inaudible] about your Tenofovir experience with a change in guidelines. What is your recommendation in children and your experience you have with any regimen change [inaudible] in children and to the transition from D4T40 to 30, is delayed until April next year.

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Is it because of stop the D4T in country or what is causing the prolonged delay to after next year, which is almost a year away and then about a comment to our Professor Gilk on the CD4. Experiences in our countries show that laboratory is still the biggest tumbling block or bottleneck to scaling up programs.

Many practitioners recognized the clinical staging and as a criteria for starting people on ARTs, the experience is that not many people actually use clinical staging to start people on ART and still rely on CD4 and other laboratory testing to start.

With the staffing capacities in our countries, it is not possible to decentralize CD4 to the lowest level health center and it might be wise for our country, for example, to stop regional laboratories and instead transport regimens the regional laboratories that are able to test and take the results backward [misspelled?] if you are going to be able to scale up rather than having every small health facility having the capacity to do CD4. Thank you.

**PETER MUTENYA:** There are a couple of hands up. Okay.

**JOHN KAPLAN:** How is that? Okay. John Kaplan, CDC Atlanta. I would like to raise a question to the group about our definition of treatment failure and it is raised to some

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respect by Elliot Raizes' presentation and also drawing on discussion even last year at this meeting.

So one point that I think came out in Dr. Raizes' presentation was that was not emphasized a lot was the difference in approach to diagnosing treatment failure in countries - some adhering to the WHO definition and some varying from it to different degrees either using different CD4 criteria or varying viral load criteria.

So Charlie, to you, last year I remember at this meeting, we had a discussion about whether there would be a new approach to try to defining treatment failure recognizing that it may be an impossible question to answer because we are in a changing landscape all the time.

We have differences in the availability of second line drugs, differences in the availability of viral load monitoring and so - but anyway, I wondered if I could get some comments about our approach to diagnosis of treatment failure. Thank you.

**PETER MUTENYA:** Let us take one more and then answer the - yes?

**BRIAN:** My name is Brian from the regional office of WHO. Two questions - one for Zambia. I think about a year ago I had the opportunity to participate in a review of the ART program in Zambia and one of the biggest challenges was the

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maintenance of laboratory equipment. Quite a few centers had the lab equipment but because of shortage of re-agents [misspelled?] and maintenance in some of the places, they were not working.

Now in regards to the use of creatinine - the test for creatinine to try and check for a renown problems, how do you plan to continue decentralizing because I know Zambia is trying to move to decentralizing initiation of treatment. How do you plan to be able to continue decentralizing if you will be so dependent on the lab or are there other plans for addressing the problem of actually lab testing at the lower level?

Then the second question to Namibia - the issue - you raised the issue of anemia where you really are beginning to have real problems, I just wanted to find out what your strategies are for actually addressing those problems strategically because you definitely do not want to continue picking up people with hemoglobins of three, four in some of them. You would actually be losing. So I am interested in hearing what the strategy is to address that problem. Thank you.

**PETER MUTENYA:** Alright, we have quite a number of questions for Zambia. Maybe we should start with you then Namibia and then we will answer something about treatment failure. Please be brief.

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**MALE SPEAKER:** Thank you very much for the questions. I have picked out four questions directed to the presentation on Zambia. The first one was the recommendations of switching from the current D4T-based regimens to TDF-based regimens. In our guidelines, it is very clear that all patients that are doing well on treatment should not be changed from their current treatment.

The drive to change from the D4T-based regimen has been mainly the toxicity issues that we have had and only then do we recommend a change to a new regimen provided there is not clinical failure or signs of clinical failure.

The reason why we have seen many patients moving, this has not been due to the guidelines' direction but rather due to just prescribed practices and also patients demanding that they are put on treatment that they feel is more superior. So this has been the driving force behind the change from the older regimens to the current regimens that we have. This was not anticipated but we have to adjust to that demand.

The second was protocols for children for ARTs. The guidelines that I have shared with you are only for the adolescents and adults. For children, we are still maintaining the old regimens that were recommended. So Tenofovir is not being used in children. As you know, there is a restriction in terms of licensing for use of Tenofovir in less than 18 years.

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The third question was the switch from 40 milligrams to 30 milligrams. Again, this is much related to the first question. If a patient is doing well on treatment, we continue even if it is 40 milligrams Stavudine that they are receiving. As you know, patients are very close to their drugs. They do not want us to interfere with their drugs just in case it affects their health status.

So since the recommendations for changing from 40 milligrams to 30 milligrams are based on toxicity issues and not efficacy, patients who do not have toxicity issues from D4T 40 milligrams are not changed directly - immediately. What we saw in Zambia is 25-percent of patients who were on D4T 40 milligrams we were switching because of the toxicity issues.

There is still another 75-percent that do not have any toxicity problems so we are encouraging these to continue but we are phasing it out. This is why the phasing out has not been immediate. So there is still 75-percent of our patients who are doing well on Stavudine 40 milligrams.

The last question has to do with our laboratory capacity issues. To begin with, the problems that we had with our laboratory was mainly not having enough reagents in most of our labs. Of course, there were equipment issues but we have addressed those by getting new chemical analyzers but that does not solve the problem of reagents. So we still have some

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facilities, which are not able to do serum creatinine, which is used in the calculated - in the creatinine clearance.

So the measures we are applying are basically to have a courier system for samples. Samples are taken to laboratories, which have good capacity in terms of the equipment, reagents, and also human resource. This is one way of solving a problem where we cannot have primary facilities having fully equipped laboratories in place. So we are using higher-level facilities to actually process the serum creatinine.

I think those are the four questions, which were directed.

**PETER MUTENYA:** Yes. Thank you. Namibia?

**MALE SPEAKER:** Coming to your question about the strategies for treating AZT-induced anemia - what we basically do is actually that we do not start anyone with an HB, which is lesser than eight. We do not start them on AZT. That is the first thing.

Obviously, most - once we have started a patient on AZT, we do frequent follow-ups with blood counts. We do them two weekly after starting them on AZT and then what we do is actually we start them - we do them monthly and then three monthly. So it is a constant awareness that patients who are on AZT have got the highest probability of actually developing anemia but in case - if they develop anemia, what we still try

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to emphasize is actually so that one must still exclude other causes of anemia.

There are chemical [misspelled?] conditions, blood losses or whatever so plus a clinical screen for that but once it is actually confirmed that it is an AZT-induced type of anemia then what one will actually do is infect most of the patients actually present in a very symptomatic way.

So they require frequent blood transfusions, transfuse them and then we monitor them on a frequent basis. If their anemia persists for more than three months then we do reconsider giving them [inaudible] and in effect, we arrange for [inaudible] to be given to them but obviously that comes at a very high cost.

**PETER MUTENYA:** Thank you. Charlie, would you like to take that there?

**CHARLIE GILKS:** Yes. I think treatment failure and CD4 counts and I might well speak about anemia if that is alright Peter. Okay. Well firstly, to the colleague from Kenya asking about CD4 counts and pointing out that I think as other inputs from the floor have noted is that laboratory is actually a major bottleneck in many countries particularly low-income countries and wondering whether transported - the CD4 of the specimen would be useful and in fact, there are several

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commercially available preservatives, which extend the viability of the CD4 and lymphocytes in a serum sample.

The trouble with this is that you are just, I think, shifting the problem upstream because you will generate very large volumes of CD4 tests that need to be done in your district or subregional laboratory and you have a problem of getting the samples from your decentralized sites regularly to the CD4 and then you have got the problem getting the results back in a timely fashion.

When Brazil started its national treatment program, it had a regional set of laboratories for CD4 counting and for viral load. Viral load was a particular challenge and it would take up to about four months to get the result back from an accredited regional laboratory. The time is reduced now but it is still of the order of weeks and I think the same thing would happen here.

One of the motivations for clinical staging for us in WHO is that we did not want people to be denied access to treatment when clinically, it was very obvious to their carers that they were in need of immediate ART and we did not want there to be any reluctance or any delays because clinically, it was obvious that you did not have the supported tests.

I believe actually though that in some countries and we have had some experiences in South Africa that some treatment

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sites do need to wait for the result of the CD4 to come back regardless of how sick or not the patient is clinically.

So I think we have to say CD4s are very valuable and ideally we would like a pretty much real time result but we do have to recognize that the programs, particularly decentralized programs, may have to rely on clinical monitoring and that there were to be much better training and refresher training for staff in what is regarded as a simple tool but in fact is quite clinically - to do it well, you have to be properly trained and supported.

John, you asked the challenging question around treatment failures. We did have a meeting earlier this year and the - around the different domains of treatment failure and we will be very soon having that - in fact I think it is up on the web already - and we did not change the viral threshold but we were more permissive in thinking about where targeted viral load testing would help particularly in the discordance that is being reported in many countries.

There are patients who are failing clinically but appear to have undetectable viral load and indeed India, at the moment, is in its - as it has now finally got the availability of second line and it is looking around what its national recommendations are of what constitutes failure. They are using viral load testing as a tiebreaker for that reason.

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I will also refer you to our recent Lancet paper about modeling the need for laboratory monitoring for people on ART and for those of you who did not see, this was a modeling exercise looking at the additional benefits of patients on antiretroviral therapy being monitored with clinical monitoring alone using the WHO staging, using clinical and CD4-based monitoring using clinical CD4 and viral load monitoring.

And I think for a public health approach, which does not necessarily have much access to viral load and CD4 testing, the results of that modeling exercise were actually very reassuring. It was 20-years survivals predicted in 68-percent of the viral load monitoring for failure and 65-percent with clinical alone monitoring. So a three percent difference at 20 years with two-thirds of the patients still being alive, which was quite reassuring.

Finally and Andrew Phillips was the first author of that paper in The Lancet about six weeks ago. Finally -just a question or a note about the question of anemia and Dr. Siley's [misspelled?] part of Peter's team in JCRC here, published the largest series of AZT anemia in HIV infected adults in Africa 3,300 patients out of the DARK trial and what was reassuring about that was that anemia predicatively - the rate of anemia was predictable maximally between eight and 12 weeks.

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After that the impact of AZT on improving bone marrow function kicked in and that you really only needed to worry about AZT anemia in the first two to three months. You could do targeted screening for it and remember, there are a variety of low technology tools for diagnosing anemia and that you could, in many patients, treat your way through it, and the numbers of people who had catastrophic grade IV anemia was really very, very low and it was about less than one and a half percent and there were only a couple of anemia-related deaths in those 3,300 patients.

It is important to note that because if people are going to - if companies are going to be using Tenofovir first line, then they are going to be using AZT second-line. So the issue of anemia is not going to go away.

In fact, it is going to become more prominent because almost everybody will need to be using AZT and if patients are going to be failing clinically, they are going to be in a similar sort of clinical state, as many of the patients who we have who are currently initiating treatment relatively sick and often quite anemic.

So the issue for AZT anemia is not going to go away with Tenofovir. It is just going to be postponed to second line. Thank you.

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**PETER MUTENYA:** Thank you. We will have just a few more questions and then I think we have - oh - we have - okay. The hands, which are up only. Do not forget, John, I think at the back there.

**JOHN ELLIS:** Okay. Is this on or not? Yes it is, okay. Now it is. So I just wanted to share some information in case it is helpful. I am sorry to use the opportunity to talk rather than ask a question but in case this happens to be helpful to any countries in the room going through these decisions right now, I just wanted to share a couple of things that were raised at various points.

So one is Charlie raised the point about formulations of boosted Lopinovir for early initiation of infants noting that there are currently only liquid formulations of Lopinovir, Rotonavir for use in young infants who cannot swallow the 125-milligram pill. So on that front, I just wanted people to be aware that we - so first of all, by way of background, I work at the Clinton Foundation.

My name is John Ellis [misspelled?] and we are working with manufacturers in India to try and develop a sprinkle formulation of Lopinovir, Rotonavir for use in infants in case that is helpful and we can share information about when that formulation might come to market and that would at least be sprinklable on-

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**MALE SPEAKER:** I think if you started using [inaudible] you will be able to, as a certification, like ideas, what would be the ideas versus [inaudible] versus we'll start at the level to end it. And also in the short and long-term by starting early, this might decrease the morbidity and mortality, which can be [inaudible] in the increasing work time or so, which should decrease the cost of ART in the long-term.

**PETER MUTENYA:** Thank you. The last two questions at the back.

**MALE SPEAKER:** I am attempted to ask our colleague from Clinton when we will have flavored sprinkles ARV for adults also but I think we would be here until breakfast hearing the answer. Quick question, considering all of the different factors with lab, with human resources, with supply, what do you each see as the rank order of rate limiting factors in continued scale-up?

Now maybe without explanation, just lab, human capacity, manufacturing response - where do you see the rate limiting factors for continued scale-up?

**PETER MUTENYA:** Thank you. The very last one and then - no, sorry I do not think we will allow any other questions. Let us have that as the last one. Yes.

**CHRIS TOFAMIN:** My name is Chris Tofamin [misspelled?] [inaudible] Nigeria. I have one question for the Zambia

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presentation as guided through very nicely through the systematic process, what it means to make those changes.

There was, however, one point was missing and that was on the one hand you were showing the [inaudible] about 50-percent of patients are need in Zambia have not yet access to treatment. How do you deal, as a Minister of Health, with the problem of opportunity costs when you start - switch those ones who are currently on treatment on the double expensive or triple expensive regimen?

**PETER MUTENYA:** Okay. Thank you very much for those questions. We will start this side. Please, are just going to make some comments. We cannot aspire to address each and every point but we could have a discussion after the meeting.

**MALE SPEAKER:** I just want to briefly comment on the representative from the Clinton Foundation. First of all, we appreciate any efforts that you can get the drug as close to the floor as possible and, as I think you alluded to, we do not know what that floor is yet but I think it is also important to understand that as you scale up, even what seems like minor differences between costs and drugs, become quite accentuated especially when you talk about the types of numbers that Charlie was referring to with these new targets.

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So I think it is just something to keep in mind but we also applaud your efforts to keep getting that drug down - price-wise. Thank you.

**MALE SPEAKER:** Yes?

**MALE SPEAKER:** I think I am addressing the principle obstacles of Botswana would face and the main bottlenecks in terms of scaling up to the universal access target. I think Botswana is in a relatively unique situation in that it has entered middle-income status and so in terms of funding decisions, although they are extremely important, it has more funds at its disposal than almost any other sub-Saharan country.

In fact, its GNP per capita is \$12,000 in the latest figures. The possible bottlenecks, however, are some that are shared by probably my colleagues at this table. Human capacity is a major one. So if you decide to treat more people, you have to have more staff to do it at every level and they just do not exist in Botswana at the moment.

I think laboratory capacity in terms of the technical issues is probably the number one bottleneck that will be faced and I think I will leave it at that.

**PETER MUTENYA:** Thank you. Just a brief comment. Yes?

**MALE SPEAKER:** Okay. I think there are three questions.

The first one is very simple. The bottleneck to scale-up is

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crippled health systems and the number one component in that is human resource as Mark [inaudible] has already said.

The other two questions, I think, are related - opportunity costs for opting to use more costlier regimens. Well in this - what we see that if we continue using D4T AZT-based regimens, we are going to have a problem of having to switch our patients to second line, which is far much more expensive and then to make matters worse, there are some patients who will not have any options for second line treatment.

So we are cutting out costs now, although it is a little bit costlier for the national program right now but in the long run, we are making savings by switching to Tenofovir-based regimens.

**PETER MUTENYA:** Thank you. Just concluding remarks, Charlie, please make it short.

**CHARLIE GILKS:** Yes. Very quickly, to Jonah's question about the challenges and the sustain of rate limiting steps. I think money is going to be in the short-term for some countries and in the long-term for others particularly if we move to earlier and less - more potent, less or better tolerated regimens.

Around HIV too, we are planning a consultation with colleagues from the Afra [misspelled?] region in the Lucifen

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[misspelled?] country with the association of West African physicians and HIV [inaudible] are co-organizing this. We hope it will happen in January.

There is an estimated - as many as 500,000 people who are either singly or dually infected with HIV too in our current guidelines are inadequate in the recommendations we make for first and for second line. So we appreciate that gap and we hope to fill it.

Finally, to the colleague who was talking about helping countries navigate their way through these very difficult choices and issues. As we produce our new round of guidelines, we will be doing scenario modeling exactly in the same way as the colleague from Zambia talked about when they were making a change to help list.

What the issues are and what the costs and the problems and the benefits of each of the different decisions and changes that may need to be considered so the countries will be able to navigate through what are really quite complicated interlinked agendas.

**PETER MUTENYA:** Thank you. I am afraid - yes, just a concluding remark. Yes please.

**MALE SPEAKER:** To the bottleneck of scaling up of programs - the main thing is actually the human resource challenges, which we are actually facing. We must admit it - we

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are coming out of countries with very few professionals who can actually deliver the goods on the long run and that actually brings itself and then on top of that, there are also some infrastructure limitations as well, which makes it in a way, quite difficult for many of our countries to really scale-up the process.

To the colleague from Zimbabwe who actually mentioned something about the benefits of higher CD4 count threshold of 350, we have truly in agreement with you that there is a benefit. I did mention it but it is also quite important not to overlook those issues, which I have already mentioned - which I just mentioned there

And I am quite sure they are in your country and they most probably are also in other countries as well and if one goes in blindly in that option, you may - on the long run - actually end up regretting it because you may create future problems of resistance for people who might have not been ready to get into that.

So that is - it is an issue of actually waiting it out and not just [inaudible] into that.

**PETER MUTENYA:** Well ladies and gentlemen, let us give a clap for the presenters [applause] and you have been such a wonderful audience. As Jonah said, we could go and discuss this issue. The interest is great and I am glad I have been the

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chair to this exciting session. Thank you very much for  
participating. Thank you [applause].

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