

**2007 HIV/AIDS Implementers Meeting: Debates:
Expanding Access to Antiretroviral Treatment to New Patients
Versus Expansion to 2nd and 3rd Line
PEPFAR, The Global Fund to Fight AIDS, Tuberculosis
And Malaria, UNAIDS, UNICEF, The World Bank, WHO, GNP+
June 17, 2007**

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MALE SPEAKER: We'd like to start this session with debate about expanding access to antiretroviral therapy to new patients versus expansion to second and third line. We have four speakers and I'd like to ask the first speaker, who will be Dr. Moses Kamyu from Uganda, to talk about the predictors of viral failure among Ugandan children and adults treated with first-line antiretroviral therapy.

MOSES KAMYU, M.P.H.: Thank you very much. I'm presenting on behalf of the Infectious Diseases Institute at Mulago in Uganda. I was given five minutes to do this presentation so I'm going to present just a few of the findings that we had in this analysis.

The Infectious Diseases Institute provides care for over 10,000 HIV infected patients. About 50-percent of them are on non-retroviral therapy. In this analysis we identified predictors of virologic failure among HIV infected children and adults. Viral load is not routinely done in the clinic so we wanted to find out whether there were some predictors in virologic failure that we could use as surrogates of virologic status. Specifically we also wanted to look at the AR2 regimens that we used in the clinic to see whether there were any differences. The AR2 regimens are the IDI provided through

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two major sources and those are the Global Fund and PEPFAR.

The first line regimens are really, largely two of them. The generic fixed dose combination of triamine D43TC [ph] therapy and the branded drugs AZT/3TC and the fibrins. Those are the main regimens that we use. So we looked at 767 patients whom we had studied in treatment and analyzed their outcomes after 12 months, one year following treatment. There are 250 children and 526 adults. As you can see one year into treatment, 66 adults had died, and 13 children, and eventually at the end of one year we 222 children and 454 adults whom we analyzed outcomes at 12 months. This is the virologic response consider on treatment and protocol analysis and as you can see these are very, very excellent virologic suppression rates. We also noted that adults responded better than children if you considered only treatment analysis and the difference was statistically significant. But overall everybody responded very, very well. This is the most important slide for the evening and I want you to look at the comparison of the regimens, comparing the generic triamine to the branded AZT-3TC of fibrins. Patients who are taking the generic triamine were 2.5 times as likely to have virologic failure compared to those taking branded AZT/3TC with fibrins. And this was the same

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ratio in children as well as in adults. And the difference was statistically significant.

So in conclusion, again remember I have five minutes, in both children and adults we observed that taking generic triammine was 2.5 times more likely to have virologic failure compared to those taking branded AZT/3TC with fibrins. And you shouldn't judge this regimen so quickly. The explanation could be one of the following. First of all, there may have been unmeasured bias because this was not a randomized trial. It might have been that the greater curability of AZT/3TC with fibrins was explained the difference significantly. It could be that fibrin is superior to [inaudible] therapy and it could also be that the generic drugs have inferior quality. But it might be a true difference between these two regimens, but we wouldn't like to say that this is definitively true that the generic triammine is inferior to the branded AZT/3TC with fibrins. Thank you very much.

MALE SPEAKER: Thank you very much. Our [inaudible] speaker is Alwyn Mwinga from CDC of Zambia and she will talk about Inclusion of a Tenofovir-Based First-line Regimen in Zambia - A Bold Step Forward?

ALWYN MWINGA, M.B.: Good evening ladies and gentlemen. I'm going to present on behalf of the HIV CAN [misspelled?]

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Treatment working group in Zambia and I've entitled my talk
Inclusion of a Tenofovir-Based First-Line Regimen in Zambia - A
Bold Step Forward? We'll try to discuss the rationale for
change in regimen by the national program.

As a brief background, Zambia has a national HIV set of
problems of about 16-percent, meaning about 200,000 people are
living with HIV and in need of ART. Way back in 2002 the
government decided to scale-up the availability of ART and had
an initial target of 10,000 people from its only sources.
However, in 2004 with the coming of both PEPFAR and the
availability of Global Fund, the ART program has expanded quite
rapidly in the country, and the treatment was based on the
[inaudible] guidelines for management of HIV in resource
limited settings. In an initial phase the ART was provided
mainly in the larger hospitals, beginning in the first phase
with three hospitals and then expanded to other provincial
hospitals and currently the services are available at district
hospitals as well as some health centers. And many programs
have developed satellite programs as well as mobile services in
order to expand their reach of ART availability. And currently
we have about 293 sites in the country and we have
approximately 100,000 on treatment at the moment. Pediatric

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places account for 6.5-percent of the total cases and currently there are less than 300 patients on second-line treatment.

In terms of the national guidelines that were developed in 2004, the first-line regimen is based on the generic triammine and second-line treatment is as we have here with tenofovir or abacavir, 3TC and 1PI ritonavir. In the national program eligibility for ART is determined by basically two mechanisms dependent on the level of healthcare, CD4 count available, and also total lymphocyte count or clinical staging where CD4 count is not available. And the choice of drugs is basically influenced by whether or not the patient is pregnant if it's a woman, presence of other illnesses that need co-treatment like TB, anemia, hepatitis, neuropathy and kidney diseases. Treatment is monitored mainly with lab tests and patients are seen initially after the first month, at three months, and then every six months after that. And it's also monitored by clinical outcomes. Viral load testing is available at a few centers but is not used widely to monitor the patients.

In 2006 a process began for revising the national guidelines based on available treatments and also the price of the treatment. The leadership for this revision was provided by the CAN Treatment Working Group of the National AIDS Council

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as well as the Minister of Health. And this revision was done as a consultative process involving all stakeholders in the ART program. And the final guidelines were approved by the National AIDS Council and the Minister of Health. It was decided that the new regimen would be applicable for all new patients and initially the date was set as May 2007, while patients who were already on treatment would not be changed unless they needed to change as indicated by either treatment failure or toxicity. In the new regimen, this is a tenofovir based regimen with tenofovir and 3TC or FTC with either efavirenz or nevirapine. And the second-line regimen was the two MRTIs and one protease inhibitor. Changing over to this regimen involved a lot of discussion back and forth and I'd like to take us through some of the reasons why we decided to change our drug regimen.

If we think in terms of the characteristics of an ideal regimen, it should be a doable regimen limiting the delaying changes to a second-line regimen as well as efficacious. You want a regimen that has convenient dosing. We know that adherence is one of the main causes for failure and so you need a regimen that reduces the probability of poor adherence. We also looked at the resistant profile for the drugs that we were using and wanted drugs that would have limited cross-resistance

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with other drugs, as well as a regimen that was tolerable and safe in order to improve adherence as well to ease the monitoring of the patients. And then, of course, finally was the issue of the cost of the drugs, not looking at the unit cost of the drugs only, but also looking at issues of cost effective considerations. When we looked at the tenofovir based drug regimen that we decided to go for, I think that there have been studies that have been published of late showing that TDF/3TC and efavirenz have better CD4 responses and viral suppression than studied in base regimens. In fact, some studies have shown that with the D4T, TTC and nevirapine within the first year about 22-percent of the patients would change their drugs because of toxicity and by 18 months about 20-percent will have failed, meaning that within two years you can expect 40-percent to have changed their drug regimen. However, with tenofovir, the one study that was published last year, showed that by three years it had a better profile than [inaudible] base.

The second concern in terms of safety and tolerability, the SENS [misspelled?] study showed a much lower frequency of side effects without much evidence of mitochondrial toxicity, while we do know that with stavudine there is problems with

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mitochondrial toxicity which includes the episodes of lactic acidosis, peripheral neuropathy, as well as lipodystrophy.

Then we looked at the issues of resistance profile. Drugs based on D4T, I won't go into all the issues of the mutations that are developed, but basically D4T does cause cross-resistance with all the other NRTIs and also in the presence of more than two mutations, you do get the cross-resistance. These mutations tend to be archived so that you have resistance almost permanently. While the tenofovir-based regimens have a lower frequency of development of resistance and the resistance is not progressive, so that you preserve your second-line regimens.

Then finally the issues of convenient dosing. We do know that there's a fixed drug combination that has not been licensed and these drugs are taken once-a-day, so bringing the prospect of increased adherence by the patients. One of the issues around toxicity that I think we are concerned about is the fact that tenofovir is associated with more toxicity, especially if the initial creatinine clearance is less than 15 ml/minute. However, it doesn't apply in patients that have normal renal function. So this may limit the use of this drug in lower levels without the availability of renal function

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monitoring. However, currently in our program, renal tests creatinine is part of the normal base-line evaluation and we would be looking at the significance of viewing proteinuria linked to renal function.

When it comes to cost, I think this has been one argument that has been raised against the use of this drug, however, we do know that as of late that these drugs have been reduced in price, and recently the Clinton Foundation together with UNAIDS negotiated almost a 45-percent reduction in the cost. So this will not apply and I was just informed today that ASPEN would be producing this drug as a generic so the issue will go away and it will be probably affordable. Especially when we look at the long durability of the first-line regimen and no one needs to change to a second-line regimen.

In conclusion, based on a thorough analysis of the pros and cons for the tenofovir-based regimen, Zambia has decided to change over to this regimen based on expected benefits to improve adherence, to the lower incidents of side effects, the convenient dosing and the long durability with the regimen with the delay in switching to second-line treatment. Thank you.

MALE SPEAKER: Thank you Alwyn. Before moving to a specific discussion, we have added two more speakers now doing

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research about this debate and I'd like to invite Dr. Daqua Hanuini [misspelled?] from Namibia. She's a senior medical officer from HIV/AIDS Management [inaudible] Team from Ministry of Health and Social Services.

DR. DAQUA HANUINI: Good evening. My name is Daqua Hanuini. I come from Namibia and I'm working in the Ministry of Health and Social Services as senior medical officer responsible for case management of HIV and AIDS. At the beginning allow me to share with you some issues concerning the choosing of ART regimens in Namibia.

Firstly, Namibia is situated in the southwest part of Africa and we have five neighbors, that is Angola, Zambia, Zimbabwe, Botswana and South Africa. We share one ocean and, of course, two deserts. Namibia is a big country in size. It's approximately 825,000 square kilometers with a relatively small population of 2.1 million people. We have a prevalence rate of 19.9-percent according to the ANC serosurvey results of 2006 and it is submitted that about 240,000 people infected with HIV, and of those 8,000 is submitted to be in need of ARV therapy.

At that ART program, in Namibia the government is providing ART treatment for free to all Namibian people who are in need. To date about 43 sites are currently providing

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treatment and 35,000 people are on treatment in the public sector. People are put on treatment according to their eligibility criteria which is clinically according to the WHO stage 3 or 4 or CD4 count equal or below 200 in adults, in pregnant women CD4 of 250 or below. And one also needs to meet the social criteria which is one needs to have a stable address where the person lives, the person needs not to be on alcohol or drugs or the person must not have an active mental illness and the person must be ready to access to treatment center because if someone is living far from the treatment center, it's not possible for this person to be adherent. The person must demonstrate commitment to care, like the person at least must come for followup regularly in the months, has at least somebody to support this person as a treatment supporter or partner.

Now how programmatic decisions are made. There is a technical advisory committee on antiretroviral therapy which is composed of senior personnel of Ministry of Health and Social Services responsible for HIV care delivery. Also, senior medical consultant from departments of Internal Medicine, Obstetrics and Gynecology, as well as pediatrics and also technical advisors in the field of HIV care and treatment, PMTCT and also TB. Also, a senior pharmacy representative from

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the National Medicine Policy Division and several medical stores. It is also having a representative from Health Information Systems and the response monitoring information unit. Technical advisor committee makes the recommendation to the Minister of Health which is finally responsible for the administration of the ART program.

As far as choosing a first-line regimen, our program started in 2003 with original first-line regimen of D4T, 3TC and nevirapine, which is consistent with WHO recommendation. But in 2005 to 2006, persons on ART started to have increasing side effects mostly peripheral neuropathy, lipoatrophy and lactic acidosis. In September 2006 the WHO new recommendation on adult ARV recommended moving away from D4T-based regimens. In November 2006 Namibia technical advisor committee on ARV recommended a new first-line ART regimen which is consisting of AZT, 3TC and nevirapine.

Why AZT over D4T? The technical committee deliberated on this question and considered the following. Even though both AZT and D4T have similar frequency, durability and pill burden and there's only a small increase in the cost of about 48 U.S. dollars per year more per patient, which is equivalent to 168 U.S. dollars per year with nevirapine and 344 U.S. dollars per year per patient with efavirenz and some concerns

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about anemia and certain side effects of AZT were also considered, but the side effects of D4T and other associated problems outweighed the costs. So tenofovir first-line regimens available also for persons who are unable to take AZT or nevirapine. Also a question was considered, why not tenofovir in the first-line? All these factors were considered because for tenofovir there's a potential for once daily dosing, with FTC and efavirenz, also the side effects were considered. And the resistant profile was studied as well as the program costs. And finally, the decision came down to program costs. Because DDF based regimen was twice to three times more expensive, which is demonstrated here like it costs about 351 U.S. dollars per patient per year with nevirapine and also about 526 U.S. dollars per year per patient with efavirenz. DDF first-line would add millions of U.S. dollars to the costs of the program. At the present moment, Namibia cannot afford this. It is too expensive for us. But should the price of tenofovir come down to the level of AZT, of course, it can be considered later as a first-line, but not at the present moment.

DDF is reserved, however, for persons with active hepatitis B virus, which is common in Namibia. Also, to touch a little bit on transitioning a person off D4T. Because

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thousands of persons on D4T are doing well with no apparent side effects, the new Namibian guidelines give specific instructions on when to transition patients who have peripheral neuropathy, lipodystrophy, elevated transamulosis [misspelled?] also the people who are symptomatic on D4T for 24 months. No person is to be changed from a D4T containing regimen without good reasons. D4T also, however, will only be available in 30 mg strength in Namibia as from now.

On the second-line regimen the decision to switch is made by the local ART committee or with a special consideration. Proposed regimens follow the WHO recommendation. As we see, abacavir plus DDI and also [inaudible] as well as tenofovir, 3TC, AZT and [inaudible] and AZT/3TC DDI [inaudible]. The second-line regimen is very expensive. The best is for one not to be infected, and if infected to stay on the first-line regimen. The second-line regimen is about six times the cost of the first-line regimen. It's almost like 1,000 U.S. dollars per person per year. It has increased in long-term side effects, of course. Also, additional many laboratory tests add to the costs.

Thirdly, we have potential salvage therapy for adults. That is [inaudible] regimen, as we see, and of course this is the most, very much, expensive, like 1,200 U.S. dollars per

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person per year. It's also complicated dosing, high profile side effects and one can expect underlying resistance which can compromise an infected person. With this I want to thank you for listening to me.

MALE SPEAKER: Thank you very much Dr. Hanuini, and the last speaker will be Dr. Charlie Gilks from [inaudible]. He will talk about the Expanding Access to Antiretroviral Therapy [inaudible].

DR. CHARLIE GILKS, M.D.: Thank you very much and good evening friends and colleagues. It's been a long day and I'd like to thank you for keeping your energies up and being interested enough to join us in this session and hopefully for an interesting debate later. So thank you very much.

I'm going to try and now give a more global view of some of the issues that we're facing in expanding access to ART and in particular the issues involving regimen options, which we've heard very clearly from three different points of view from the implementers who are facing a discussion about whether they should go for brand or for generic, from Zambia which is thinking about moving towards a tenofovir containing regimen and from Namibia who decided, faced with similar information, to stay with thymidine first-line.

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Just to orientate to where we are. There are more than two million people globally now on antiretroviral therapy. The provisional figures for March this year is about 2,300,000. All of these patients, almost all of them in low middle income countries are adopting the strategic approach that we at WHO have been promoting, which is to use a public health approach to antiretroviral therapy. And I hope many of you are familiar the recent *Lancet* article which outlined this. And essentially we have to promote universal access to ART, taken whatever evidence is there, simplify it and standardize the recommendations. And critically within that, as we've heard from everybody, there is one first-line regimen with substitutions for toxicity or drug-drug interaction or potential to retrogenicity [misspelled?] and then with treatment failure a switch to the second-line regimen. That has been based around the three different classes of drugs that are orally available and relatively cheap.

The treatment policies are laid out and these are the front covers of the 2006 revisions of the Treatment Guidelines for Adults on the left and the blue one is the new Pediatric Stand-Alone Guidance, which is just about to come out in hard copy and has been on the web for several months.

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I'm just going to talk about some of the issues around adult and pediatric treatment that countries are facing in trying to choose optimal regimen for their circumstances, and clearly there are a lot of issues around populations in need, costs and the availability to implement potentially toxic treatment.

This diagram summarizes the current recommendations for adult and adolescent first-line therapy. The core drug remains 3TC, but that has now been added FTC, which is regarded by us as an equivalent drug to 3TC, more expensive, but an exact equivalent in toxicity, potency and its place in the treatment. Previous guidelines just had AZT or D4T, a thymidine analog, which is the second NRTI, which would support efavirenz or nevirapine as the two NNRTIs. The new 2006 guidelines widened up the option for first-line by including tenofovir or abacavir, which had previously had been considered either not appropriate or were reserved just for second-line. We put those in because there are clear advantages in some circumstances in starting with more expensive, non-thymidine analogs rather than the thymidine analogs in terms of tolerability and in terms of the ability to have much simpler dosing, and indeed in some combinations once-a-day dosing with one pill. I do have to say, though, that the data to suggest

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that tenofovir or abacavir non-findings along the first-line are now more potent, we don't actually have that data there. Many companies are saying these are more potent, but I do think we need to have some caution in recognizing that the data do not support statements to suggest they are more potent. But they're clearly going to be more tolerable.

So the main issue for countries for adult regimens, as we've heard the different choices face Namibia or Zambia, are to whether to move from the really quite toxic stavudine or D4T with the interim measure for dose reduction just to using 30 mg to either going to AZT or tenofovir or abacavir first-line. Both of these options are associated with additional costs for the medication.

Just to show one slide to show that in Africa and in many, but not all, middle income countries, most adults are on a 3TC/D4T containing regimen and the majority in this part of Africa are using nevirapine as the NNRTI, whereas if you go down to southern Africa, the choice is more for efavirenz. Efavirenz is a more expensive of the two NNRTIs, as we heard from some of the cost data that Namibia is seeing in their program. But essentially, almost all low-income countries have adopted the WHO guidance and are using a 3TC or D4T regimen and there is some regional differentiation. In Asia and South

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America it's a similar story, although in Brazil, there is more use of a protease inhibitor as initial therapy.

So where are we with first-line ART? I've just summarized the choice that some countries are facing and they are moving towards tenofovir with FTC, which is the branded and approved preparation, or tenofovir with 3TC, which is another alternative, but there are no generic pre-qualified fixed dose combinations yet that countries can purchase for this. There are some in the pipeline, but none yet have been pre-qualified by WHO, and certainly none have been approved by FDA or EMEA. It's been almost no use of abacavir in adults, and there's certainly been almost no use in the NNRTI regimens, which is an alternative that the new 2006 guidelines do allow as an alternative regimen. We're not sure what's going to happen with the recent EMEA class 1 withdrawal of nelfinavir. This nelfinavir is relatively widely used in some PNTC programs, and we're going to wait to see what countries opt for, whether they go for nevirapine or whether they start at least with pregnant women with higher CD4 counts going for safer and more tolerable but much more expensive option of the abacavir.

Certainly abacavir is the preferred option in children. We cannot use tenofovir, so if there's any discussion or

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consideration in starting with a non-thymidine initial regimen in children, one has to opt for abacavir.

What about second-line? Now this is what the current guidelines recommend and I will immediately qualify this by saying it looks quite good, but it isn't actually that practical to use at country level. We've had several discussions recently, unbeknown to quite a lot of pressure, to be more precise and to prioritize out of this potential complexity. And the two issues that faced us are, what is the optimal choice of the two NRTI supports that will support a boost protease inhibitor and then out of the four different protease inhibitors that we considered in the guidelines, which would we prioritize. Recent report on treatment scale-up we issued March this year, which was reporting on progress for 2006 where we reported that over two million people were on treatment in lower middle income countries, only 40,000, that is two-percent, are actually on second-line at the moment. There is, unfortunately, very limited provision in this in the public sector. And whilst we've recently re-echoed the point that universal access to everybody should include access and provision of second-line, at the moment because of complexities in regimens, because of cost, there is limited availability. And the costs are anything from 1,000 to \$2,500 and even higher

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costs in the middle income countries which don't have the preferential pricing agreements that many companies have made. It's even worse than that when you consider that 30,000 of those 40,000 just in Brazil where there has been a long-term commitment for second-line. So really there is a big problem in scaling up access to second-line. Part of it is the current complexity of guidelines, and that is inhibiting consolidation of the market around one or two preferential products which can then have aggressive pricing reductions and can take an expanding market where we will really see competition and reduction in price.

We also have problems with second-line with the HIV/TB comanagement, particularly the problems of using [inaudible] with boosted PIs, and we didn't find any countries where they were reporting any children on second-line. So the problem for children is even worse when you look at those who are failing first-line.

Currently there is a very wide use of second-line regimens. The most widely used is abacavir and DDI with lopinavir boosted by ritonavir, which is one of our favored regimens. That is actually really quite expensive because its got abacavir and the lopinavir, and this lopinavir will be replaced by the heat stable alluvia [misspelled?], and then a

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whole variety of other recommended first-line regimens, and this tells us several things. Firstly, that there will be little market consolidation when there is such heterogeneity of response. Secondly, those countries really are not clear, and we have not been clear enough, on what the best options are that are available and can be produced in our guidelines.

It's also clear from modeling exercises that we have done in WHO, and this graph actually comes from a modeling exercise that MacKenzie [misspelled?] did for the global fund, that the need for second-line will increase. We've been seeing success, and if you remember back to the first slide I showed over the last three years the increase in numbers, we're predicting a switch rate from first to second-line of between four to five-percent annually. So the need will go up. If we don't reduce price, up to 80-percent of the current costs of treatment of a cohort of patient started this year, in five years time, will be taken up by purchasing a second-line for the 20-percent who will need treatment in five years time. So if we don't have price reductions, we're going to be in a very difficult position.

What have we done? We've tried to prioritize the ART options that exist. And we had a meeting three weeks ago. I'm not able to show you what the recommendations of the meeting

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are because we haven't finalized them, but we're close to being much clearer about what the prioritize recommendation for the NRTI component is, and we've looked at that in two ways. We've called the majority use, which of those who have started with thymidine analogs and we will be making clear recommendations for two NRTI drugs to be used to support the boosted protease inhibitor. We also had an interesting discussion to think about the future when people start off with non-thymidine analogs as first-line. And we're also much clearer about which two boosted protease inhibitors we would be recommending as a priority product. With that, we really do hope that the market will consolidate and there will be increased access and the costs will reduce around a more restricted formulary.

We've done this process with children, and this prioritization process focusing around a few priority products has already happened, and we hope this will achieve the same two issues for adults' second-line therapy, that's to try and increase access and help to reduce costs. But also the critical issue, is to actually get pediatric appropriate products out there in the first place, because there are very, very few of those for programs as they scale-up.

So this what we did for pediatrics, I'll skip through these because time is short, but essentially the green is the

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urgent and this is the fixed dose, which is probably the more relevant, and it does include lopinavir/ritonavir as a single prioritize second-line agent. I can't show what we've done for first-line for adults, as I've said, but we will have that up on the web, we hope, in the next three weeks.

So my final slide. What of the emerging programmatic issues that I think we can perhaps start to discuss here? This issue of first-line durability and tolerability versus cost. We've heard that programs that have cost the cheapest but the least desirable option with the 30 mg D4T, 3TC and nevirapine, generically you can get that now for \$121 annually. Many of the global estimates that have costed treatments scale-up towards universal access have used this very low price. Now this is not going to remain widely used by countries. We've heard what Namibia and Zambia are doing. They're going to phase this regimen out. We heard the interesting figure of, I believe, it was \$49 additionally for replacing D4T with AZT, maintaining thymidine analog as the first-line. So there will be some cost increase even if the simple move to AZT to replace D4T happens.

What happens if countries do what Zambia is going to be doing, moving over to tenofovir FTC efavirenz? The lowest price at the moment that's out there, and this is for the Gilead

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compound, is around \$500 annually. Now we believe that this will come down in price. Efavirenz is much more expensive than nevirapine and if you have the one single, fixed, triple-dose, you have to use FTC, you have to use the Gilead FDA approved compound. That possibly can come down to about \$350, but whatever it's three times more than programs have bargained for in their costs. So there is going to be a major tradeoff here between how much extra you decide to put into first-line. Many of us believe first-line is your best option, and we should be investing more heavily in better, more tolerable, and we hope more potent initial first-line regimens. But there are major, global financing issues around this. We also do have the second problem, is if the world very quickly moves over to tenofovir we don't have the raw materials to scale-up rapidly and massively towards major use of tenofovir first-line. We would have problems in the production in the APIs, the raw materials, and we would certainly have problems in the numbers of pre-qualified or brand companies who'd be able to produce tenofovir.

So that is one major problem. I think with our prioritization exercise and the commitment from the manufacturers who do pediatric drugs, that we will have soon appropriate pediatric products in the appropriate dosing, both

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single and fixed dose combinations, and that as these come and there's a limited number of them, but there is a volume for production that availability access will increase and that costs will fall. But I think they will always remain relatively more expensive than the adult equivalent compound. So children numerically will remain more expensive as a unit cost for programs to treat.

And then the third point, and I just put this in because we've heard from Namibia some of their choices about what they are faced within salvage option, is that we do not at the moment consider salvage options in our public health approach, which is a very sparse first-line, second-line, and then stay on the failing regimen even if you have resistant virus. There are opportunities, there are new developments out there, and we are considering a strategy in our next set of guidelines is to reserve some of the new protease inhibitors, particularly darunavir and tipranavir for third-line, and we're also unclear about where the new classes of drug, the CCR5s and perhaps the intergrade inhibitors come in and how those new classes of drug will increase our options to provide first, second, and particularly, salvage regimens. But the one caveat about that, though, is that salvage therapy is going to be very, very much more expensive even than second-line. Namibia

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was talking about a five-fold increase, and that's by adding in the one single new drug indinavir. If we use the ritonavir and tipranavir as already widely being used and marketed in North America and Europe, the costs maybe around \$2,500 per year per patient. We haven't had much detailed negotiation about price reductions for these drugs. So there are issues around considering salvage or third-line options. So I think those are some of the issues we can discuss in this debate. Thank you very much.

MALE SPEAKER: Thank you very much Charlie. After these four presentations I'd like to open the floor for the audience. The microphone is there, please go to the person there and identify yourself before [inaudible] your question. John?

DR. JOHN KAPLAN: Okay, thank you. I'm John Kaplan from Atlanta, U.S. and thanks for the presentations. I have a question for Dr. Kanya as we don't want to leave his presentation behind, and then in the spirit of the debate I have about three questions for Dr. Mwinga. So first of all, Moses, I'm sorry you were limited to five minutes. Obviously your data justified more time than that. One of your main findings was that there was a higher failure rate in people who were on a D4T regimen versus AZT. Now you make a very

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important point, this is not a randomized trial and we don't want to leave the audience with the conclusion efficacy-wise the D4T is worse than AZT, but I wonder if you could say more about that finding? It might be confounding, and you mentioned that, the choice of which people are on a D4T regimen versus AZT. For example, one of your risk factors for failure was being a man, is it possible that more men were on D4T? So perhaps you could answer that.

Now for Dr. Mwinga, in the spirit of this debate, I'd like to ask you three things about the choices that were made in Zambia. One is you mentioned costs, but obviously didn't go into in detail about the cost implications down the line, so in light of Dr. Gilks' comments I wonder if you could say more about, for Zambia it's a lot of people on therapy in the next few years, so what the cost implications were. Also, you made the point that one of your arguments for tenofovir regimen was a lower rate of switching to second-line or therapy or a delay in switching to second-line therapy. But I wonder if we really know that in the African context. So if I wonder if you could comment on that. And then the third thing is about measuring creatinines. You do it routinely in Zambia, but there has to be some costs associated with that and some implications for

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other countries. So could you comment on creatinine determinations, also. Thanks.

DR. TOCOMO: I'm Dr. Tocomo, the head of HIV and AIDS unit of the Ministry of Health, Malawi. I'm impressed by Zambia for your move to go that far. My question is has there been a HIV drug resistance [inaudible] done in Zambia before making your choice? Thank you.

DR. ROBERT SPEERY: Thank you. My name is Dr. Robert Speery from AID Relief Program in Kenya. I have four questions. I'll be very brief because I know you need to do most of the talking. My first question is to Professor Charlie Gilks. When you are talking about the options for first-line treatments in Africa, are you considering the use of ciprofloxacin [misspelled?] especially for PM institute done extensively and I'm sure you have data to share with us on this issue? The second question goes to the issue of tenofovir and its severity. We know very well that it has been shown to be a safe drug selectively [misspelled?], but I wonder if you could comment on the issue of when using TBF with PI, protease inhibitor. [Inaudible] especially in [inaudible] in that context. The other question goes to the gentleman from Uganda, which is Moses. You are comparing D4T and the benic [misspelled?] drugs. Let me not speculate as you say, but my

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main concern was that adherence was the most important aspect for viral suppression. Now patients who are taking D4T, fixed dose combinations, who are actually taking fewer pills than those who are taking the AZT. So I would have expected that maybe adherence that I believe in the west for the banded ARM [misspelled?] as opposed to the other ARM. The people taking more drugs are actually better [inaudible] than the issue of combo of two drugs. I'm sure studies have done regarding findings in VRP and I think we have answered that question in terms of potency. My last question is the issue surrounding what Zambia is doing and what Namibia is doing. I think in all honesty, the choice of first-line and second-line, this is not a new debate. This information has been with us for many years. And what I think what we should be addressing right now is to what extent does evidence best medicine affect people [inaudible] in Africa. I think that is where we are lagging behind. Sometimes we are five years behind what has been done elsewhere. For example, if your moving from D4T to AZT as second-line, I mean, all those thymidine analogs and if it's really bad for failure, we know very well that some mutations have been related, so I don't know why you want to take this debate, but my feelings are that we need to focus on how can we ensure that evidence best medicine is going to influence

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clinical practice in Africa as opposed to moving around guidelines and [inaudible] to actually have the answers to some of these questions. Thank you very much.

MALE SPEAKER: Let's move first round of answers.

Please Moses.

MOSES KAMYA, M.P.H.: Thank you very much. You know the invitation I received said you have to present in five minutes, we'll be very strict on time. So I had 15 slides and I had to just choose just a few of them. But really there's a lot of data that I have not presented.

But specifically making some comment on why we think that D4T regimen performed worse, the fact is that we really do not know. We think that probably people tolerated this regimen less well than the AZT regimen, but we didn't document that for certain. And again for adherence, our adherence rates are very high, they are all over 95-percent and they were not different between the two regimens.

Now with regards to comparing the therapy with efavirenz with one is better than the other, of course, I know the NN trial did not find this in the RTIs different, but there have been some studies that have found efavirenz to be a little superior to nevirapine. Whether that was what happened in our case I really do not know. But I think, also, not all generic

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drugs are the same. I think we need some pharmacology. We need to some do some local kinetic studies to find out whether some of the generic drugs we are receiving have less viral viability compared to the branded drugs. But I cannot explain this finding for sure.

ALWYN MWINGA, M.B.: Thank you. I'll tackle Charlie's questions first. I think the first one was on cost indications, and I think when the national program looked at the issue of cost indications, didn't only look at the cost of the drug itself, but I think the total implications of the regimen that we're using. And while we do appreciate that currently the cost would be more, I think in the anticipation of reduced prices, especially, I think, after the announcement from the Clinton Foundation and UNAIDS that they were able to negotiate a reduced price. And then looking at other aspects of the program. For example, we are trying to take the ART down to the lowest level, and when you're thinking of monitoring of the patients, when you look at the D4T regimen with issues around lactic acidosis and lipodystrophy in terms of managing the side effects, with the lower side effect profile of tenofovir, it looked like overall we would be able to do better with the tenofovir than with the D4T regimen. So everything was taken into account, even the resistance profile.

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The issue about delaying in switching. I don't think we have very specific African data, but when we looked at the implications of D4T on opposing cost resistance with the drugs that we had in the second-line and since in our program viral load monitoring is very, very limited we go more on clinical failure which we know is the last stage. The program thought that in the long run we would save money by having a more robust first-line regimen and delay moving onto the second-line regimen which is more expensive and needs more closer monitoring.

Yes, I think the issue of creatinine clearance is one that we are looking at. And currently the program is going to base it on creatinine, serum-creatinine, and then use a formula for creating creatinine clearance, so we're not expecting people to be able to do the creatinine adherence but use a formula. Obviously that's going to have an impact on the level of care, but the program is trying to ensure that at least the basic biochemistry monitoring is available at district level hospitals. So where you have care being given at a clinic, they would use a district hospital lab. So at the same time we're strengthening the capacity of the labs to provide the monitoring.

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In terms of resistance, no we haven't done any resistance [inaudible] but we're in the process of setting up a program to actually monitor resistance.

MALE SPEAKER: Charlie?

CHARLES GILKS, M.D.: Thanks. I address three specific questions. The first. I just want to make some comments about tenofovir, because John and I were having an interesting discussion yesterday. There is some good safety data about tenofovir in Africa, and in particular the DAR trial, but the problem with the safety data, many of the safety data on tenofovir, it's actually on adults who've been pre-screened for elevated creatinine or urea or an estimated creatinine clearance. So what countries may do is end up putting a barrier, which as Alwyn was saying, which do a urea or creatinine, a biochemical test. Now the problem with that is, is that you may severely restrict entry onto your initial first-line regimen if you can't actually do a creatinine or a urea. The sad fact is that whilst CD4 counts are limited in Africa, they're more widely available than reliable and reproducible chemistry. And we've got to be very careful here as we were if we are going to move to wide availability of tenofovir not to exclude people from that because we can't actually measure a creatinine. We were very careful in the

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wording around clinical initiation of antiretroviral therapy as we started three by five. We would prefer CD4, but lack of CD4 was not an obstacle or a barrier or an impediment, rather to that person starting treatment. And I think we've got to review very carefully the recommendations and the tradeoff of starting someone on tenofovir who may not have access to a serum-biochemistry.

The question about single dose nevirapine. Very important. We are very clear in the PMTC treatment guidelines, that when you're not treating the mother for her own health with triple combination therapy, that we would prefer for prophylaxis long-course AZT and nevirapine supported by AZT and 3TC in the infant. We see single dose nevirapine as an interim substandard intervention, where as an interim nothing else can be delivered but one shouldn't really remain with that. And I'm a little concerned that I've heard at least one presentation in this meeting in the PMTC session where it seemed that the country and one of the PEPFAR funded SCALAP programs was remaining with single dose nevirapine as the given. I'm not saying we will start with this. This is interim, it is substandard, it would never, ever be used in the U.S. or Europe. And that that program is content to leave single dose nevirapine there. It's better than nothing, but it

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isn't good enough. I think we need to be very clear for that and a lot of the resistance issues stands for the kids who break through and for the mothers who get saddled with archived nevirapine resistance will be really quite extensive if single dose nevirapine is widely used. And I feel rather strongly about this. I do believe it is substandard therapy.

The second issue. I'm not sure about the tenofovir safety issue with it being used with the protease inhibitor. We're unaware of any major interactions and tenofovir, most of the initial licensing was done as a second-line support with protease inhibitors. So I'm not sure what your question was about, so perhaps we can talk about that later.

The third question about the lack of evidence base to impact treatment guidelines in Africa and actually in Asia is really, really very difficult. If you go through treatment guidelines for adults and children, you will see a lot of it is actually expert recommendation rather than the much higher grade which is based on cohort analysis or clinical trial data. I think this makes it really very, very difficult. We are where we are and if we set up the relevant trials now, we'll still have at least three to five years when we're going to have to make expert informed decisions rather than having the trials data. So we're trying to do the best we can, but it is

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an imperfect world that we live in. We're clear in our guidelines where the evidence remains and we're increasingly using the strength of evidence in all the guidelines that we produce in the HIV department.

I think there's one particular issue I think we do need to be aware of now and be concerned about. And that is the development of new classes of drug, particularly the intergrade inhibitors. I think many of us think these are very exciting and they will open up the possibility of an extra class of oral and perhaps a potentially quite cheap drug. I'm really very, very worried that the manufacturers of the intergrade inhibitors are only going to do the necessary trials in resource rich settings, and that we will be a long time evaluating evidence done in the wrong context trying to see how that new, very potentially promising class of drug will ever be used in Africa or Asia. And I think we need to lobby really very, very hard the manufacturers and also some of the implementers to start saying we've got to think about how these fit in now into treatment expansion programs. Because treatment options even with a first-line, second-line approach would be radically different, much easier to do if we had two classes of drugs first-line, and then we switched to two very different classes of drugs second-line. A lot of the issues

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around resistance and whether you switched early or late would go out the window if we could produce and have second-line therapy two new classes of drug. There is a declaration from the International Aids Society Sidney Meeting coming up, which emphasizes the need for appropriate research. It doesn't spell out the intergrade inhibitors, but it's part of the reason for the declaration. I urge you to find it on the web and sign up to it.

MALE SPEAKER: Just to comment regarding this question from the tenofovir and PI interaction. There is some discussion, in fact there are some data in the literature that [inaudible] even contradictory. And there is no evidence that there is clinical impact of this potential interaction that can occur. Then for a while, I think, there is no specific recommendation to use a different dosage when using both drugs together. There is another question in the audience? Here please. And of course, sir, the panelists can also make questions.

ANIL SONI: My name is Anil Soni and I work for the Clinton Foundation. I actually just wanted to share a bit of information to supplement the speakers. And first of all, I can only say that it's very heartening to see a number of countries move toward better therapeutic options with the

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support of the WHO. From our part, we are trying, as a couple of speakers mentioned, try to inform this process with information from the supply given what we do to lower prices and accelerate the pace at which new products are made available. So for those in the audience, even though it is late at night, I'd like to share a bit of information but also say that I'll be presenting on this, I think, as a natural complement to this presentation, tomorrow at 3:45 p.m. in a procurement workshop. So a few highlights of what I'll say tomorrow.

First of all, a bit of information on prices. A couple of prices were shared, I think Charlie you were referring to the WHO pre-qualified prices, it was mentioned we announce prices, President Clinton announced new prices for some of these products last month. So just to share those, because I think they do inform the planning process. The AZT triple for first-line is now to \$174 under our agreements, and I know many procurement agents whether they be SCMS or otherwise can quickly access those prices. And that's a much smaller difference from the stavudine based first-line. The tenofovir combination, and here I refer to tenofovir combined with 3TC and efavirenz because we have followed the WHO's guidance on the clinical equivalents with 3TC and FTC, that three drug

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combination, which we think is very exciting, is now down to \$339. And I'll get to the pace of quality assurance, but in terms of pricing the suppliers with whom we partner will already sell at that price this year, and we expect to lower it further. Now I should caveat that by saying that combination of three drugs I do not believe will ever be down to the same price as the stavudine combination. But I do think when it gets down to under \$300 and potentially down to \$200, you will see from a cost efficacy point-of-view equivalence because, as was mentioned, a more durable regimen and therefore over the long-term we feel is actually more cost effective. And so for those countries who are concerned about the price of that product, I think that trend is important and that price is important.

Secondly, a point on quality. As I think everyone knows the AZT based first-line combination, the three-in-one, that's already approved. The tenofovir three-in-one, that's actually going to be submitted, in fact, in the next couple of weeks to both the WHO and FDA. And four manufacturers will have that three drug combination submitted by the end of year. I think the pace of WHO and FDA review hopefully will allow this to be WHO/FDA approved very quickly from a number of generic suppliers.

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Third, a point on capacity. Charlie, just to respectfully disagree with you a bit on the capacity. We have spent a lot of time with the manufacturers going through global demand forecasts through the end of the decade, which we've done in partnership with the WHO and UNAIDS and they are quite confident that the capacity for some of the products like tenofovir will be there, in part because of the ability to change capacity from one product to another. On tenofovir, by the way, there will be eight manufacturers who've submitted to the WHO or FDA by the end of the year and so they're really gearing up upon capacity.

Last point, fourth point, I'm coming back to my first which is on prices. And here I want to emphasize a couple of things that are quite important. Prices do not depend solely on volume. And one of the things I'll mention tomorrow is that there has been an increasing trend since 2002 to buy at the lowest price, and there are risks in that in terms of quality assurance, which I'll speak about tomorrow. But also what you see there is uninformed purchasing. The intrinsic chemical composition of some of these products determine how cheap they can be, and therefore, it would be inaccurate to assume that a price curve goes down to \$0, right, and therefore for some of the products we've been discussing we can assume the prices

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will go lower but I think it is important, and this is one of the things we're trying to communicate, where the prices will flatten out. Because that's ultimately how countries can plan for long-term costs of their programs. In particular, there are important implications of product choice in the cost of treatment. And I'll mention two here, which I think are perhaps the most important to long-term treatment costs. One is the choice of 3TC and FTC, which Charlie mentioned, as the WHO recommending as being clinically equivalent. FTC is actually dosed less per day at 200 mg versus 300, and they're chemically very similar, but 3TC has an economy of scale that will allow it to always be cheaper than FTC. And therefore, for countries considering the choice of those two products, I strongly encourage you to go to the WHO and seek out the guidance on the clinical equivalence of these products because 3TC will be cheaper, period.

Secondly, and this goes to second-line treatment, the choice of boosted protease inhibitor. Ritonavir/lopinavir will never get very cheap and I say that having spent the last two years working very hard on reducing the cost of this product. Even if every patient on second-line by the end of the decade, even if half-a-million patients were using lopinavir/ritonavir, it will not be as cheap as atazanavir/ritonavir. Very few

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countries are considering atazanavir today. I think the new WHO guidelines will help prioritize some of the protease inhibitors, but to share, atazanavir is a dominant protease inhibitor. I'll just finish really quickly. I just think this is an important point, so if you'll indulge me. Atazanavir/ritonavir will be much cheaper than lopinavir/ritonavir and that will be the key to reducing the costs of second-line treatment. So for countries who are considering how to sustain the costs of second-line treatment, that choice of product will be very important. Sorry for going on so long.

MALE SPEAKER: Thank you. Please?

BART NEFERTA: We work with the Clinton Foundation in Namibia as well. My name is Bart Neferta. I'm a technical advisor for the CDC in Namibia and we work with the Clinton Foundation. They've done some great stuff for us in Namibia. Your talking about the future. We're living in the know and we have to make these decisions for our patients now. So it's great, come back to us when it's there. No, well yes you can, as far as I'm concerned. But we're in the know.

MALE SPEAKER: Just click it.

MOSES KAMYA, M.P.H.: Sir, I [inaudible]. You know we are still in a phase of putting out the fire. I mean in most

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of our countries we have too many people lined up to begin
therapy and whenever we think of these drugs we think in terms
of costs rather than safety. But on the other hand
[inaudible]. We now have our treatment plan which is one pill
a day.

[END RECORDING]