

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

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FEMALE SPEAKER: Now we are going to change the format slightly and there will be a panel of speakers, and if the panelists could come up to the podium up here and sit and each of them will present for five minutes and then we will open the floor up for more discussion, and then we will start.

MALE SPEAKER: Good afternoon, everyone. Since the introduction of highly active antiretroviral therapy, morbidity and mortality due to HIV infection has depleted dramatically. However, given longtime treatment with antiretroviral therapy, adverse effects are becoming increasingly important challenge for patient management. Side effects not only result in significant morbidity, but they also promote non-adherence and treatment failure.

In my presentation, I present findings on 406 adverse drug reactions necessitating change in first-line regimen in 389 Rwandan patients. First of all, I would like to show you the drugs used in first-line regimen in Rwanda. You see that the difficulty is included in first-line regimen.

The choice between this is largely [inaudible] in hosts and availability with donor programs. In general B14-based regimens are less expensive and, therefore, most frequently prescribed in Rwanda. If information on adverse

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effects, severe enough to switch antiretroviral therapy while systematically collected at two health facilities in Rwanda from February 2003 to February 2007, cumulatively in total 1,614 patients were on first-line regimen at these facilities during this period. Adverse effects were experienced by 24-percent of all patients in sample.

In total, we collected information on 406 adverse effects requiring broad changes in patients. Stavudine, by far, produces the most long-term adverse effects, including peripheral neuropathy, possibly lactic acidosis and retro atrophy. This rate of effects is of particular concern given its poor deface ability [misspelled?] and potentially stigmatizing nature due to disfigurement.

But Zidovudine, Nevirapine and Efavirenz all produce severe adverse effects as well, ranging from anemia that necessitated blood transfusion in some cases, rash [inaudible] syndrome and its psychological disorders. Effect from [inaudible] drugs tended to appear shortly after treatment initiation.

Again, I wish to emphasize the importance of study in producing serious adverse effects. Eighty-three-percent of all adverse events of [inaudible] are due to this drug. However, [inaudible] analog drugs in general are associated with serious metabolic side effects, according to other

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studies.

Therefore, when possible, we will commence to avoid studies being in live patient and switching to Abacavir or Tanafodine [misspelled?], first line regimen experienced patients. Studies shows that such treatment reaching to Abacavir or Tanafodine is associated with Grudwell recovery in lipid profile in general and peripheral effects in particular.

If the person is with the hosts, then the consideration should not be limited to the cost of drug alone. All related costs to managing adverse effects including life treatment conditions and psychosocial cost for patients should also be considered.

Other option would include reducing dosage of the B14 in patients with body weight greater than 60 kgs. This reduction is to initiate patient on different the B14 containing regimen's and then after a few months, proactively switch to Abacavir or Tanafodine, this regimen to avoid delay metabolic side effects.

To facilitate rapid scale-up of treatment, it is [inaudible] a pro host for the oldest anti-drug HIV and HIV drug one needs. However, it is only now with the use of this drug that several longtime side effects are being revealed.

Our second recommendation therefore is to institute a

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national pharmaco-viligence register in order to protect or respond to adverse effects.

Finally, with a command to collect from pharmacoepidemiology for studies in order to determine this factors for Rwanda's patients. I thank you very much.

[Applause]

FEMALE SPEAKER: Thank you very much. We are going to hold questions until our three panelists have finished their presentations. Our next presenter is Lillian Kocholla from Kenya. She will be presenting reasons for switching highly active antiretroviral therapy regimens among HIV/AIDS patients in low resource settings. Thank you.

LILLIAN KOCHOLLA: Good afternoon, ladies and gentlemen. My name is Lillian Kocholla. I work at [inaudible] hospital in Nairobi, and I am going to talk about fitting of ART regimens but at Mbagathi District hospital, which is a low-resource hospital setting in Kenya.

This study was conducted in association with Dr. Rhangi [misspelled?], Dr. Kusuu [misspelled?], Dr. Mwangi, and Dr. Michael Flor [misspelled?]. The HIV problems in Kenya today is at 12.9-percent, and the people that need treatment in Kenya stand at 263,000.

I am sorry. The problem is at 12.9-percent and those that need treatment currently is at 263,000, and out of

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these, we are currently giving treatment to 144,000.

Mbagathi District hospital, which we are talking about today, is a 200-bed capacity hospital, which serves mainly the slums of Kibera, which is a high-density slum in Nairobi with a population of about 700,000.

The HIV clinic in Mbagathi opened in January 2003 with support from MSF Belgium, giving both technical and commodity supplies support. As March 2000 this year, nearly 4,000 patients on ART using the current national guidelines.

As the treatment programs are scaled up, we have had an increasing number of patients experiencing ART treatment changes and we looked at studies done in Kenya and South Africa, which showed in Kenya we had 10.7-percent needing switches.

This is a study done in Kibera by Umbras [misspelled?] and presented at the Toronto Conference last year. And in South Africa we had 11.9-percent - at Mbagathi, we had 10.8-percent requiring switches after two or three years of ART.

To improve patient care therefore, we felt there was need to understand the magnitude of the treatment changes and to identify the reasons that necessitated these changes. So what method did we use?

We did retrospective review of clinic and pharmacy

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records to determine the reasons for regimen switches for these patients who are looked at from January 2003 to December 2006, and that extraction and analysis is done using MS Excel and SPSS respectively.

Descriptive statistics was done to determine ART regimen at the start of therapy, reasons for change of regimen, ART regimen after switch and ART regimen at start of therapy was a reason for regimen switch.

Our findings were that out of 4,000 patients who are on ART, 464 of them or 15.6-percent had regimen changes according to guidelines. You can see in the PIE chart that there are adverse drug reactions represent 10.8-percent of the changes as I mentioned earlier.

Treatment failure represented 1.4-percent. And then we had changes for which reasons are not documented from our records, and in 84.4-percent of the cases there was no switch.

Our other findings were as follows. We looked at the regimens at the start of treatment in the 624 patients and we found that 83-percent of them has Stavudine based regimen at start. Twelve-point-seven-percent had HST [misspelled?] based regimen and the other regimens representing 4.3-percent.

Out of these patients that were switched, we found

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that 42.7-percent of the patients were switched to HST-based regimens, 32.8 were switched to TBF-based regimens and the patients in treatment failure were all switched to Laponivir [misspelled?] [inaudible] based regimens.

We then looked at the issues that necessitated the changes, and in our settings we found that like with [inaudible] dystrophy was the main reason why we needed to change the presenting 65.8-percent of the patient. The patients, in this case, are now 486 and this is because this is what we were able to get from our files and our pharmacy records.

Eleven-point-one-percent of the 486 that represented treatment failure and so on, as you can see from the slide. We also looked at the time to regimen switch, and, as you can see, in majority of the cases we needed to switch anytime from six months to 18 months, and I think it is all explained there on the slide.

So what are our conclusions and recommendations? ADRs were the primary reason for regimen switch for [inaudible] dystrophy, accounting for almost 25-percent of all ADRs. There is insufficient documentation, however, on reasons for regimen change.

Four hundred eighty-six out of 624, which is 78-percent, of the records had adequate recommendation. The rest

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did not. So our recommendation is that long term use of B14 based regimens should be reviewed in our national guidelines and we should also strengthen systems for monitoring regimen switches at facility and national level with special attention to adverse drug reactions.

I would like to acknowledge support from the Minister of Health, the National AIDS and Sexually Transmitted Infections Control Program, Mbagathi District Hospital staff, MSF Belgium, as well as MSH RPN plus technical staff who made this presentation possible. Thank you.

[Applause]

FEMALE SPEAKER: Grace Magembe and Paula Braitstein are unable to present. So our final speaker for the panel today is Eugene Messou from ACONDA and he will be presenting main reasons of modification of the first line antiretroviral regimen in adult patients who initiated care in the International Family Health Initiative in Abejwa Detwau [misspelled?].

EUGENE MESSOU, M.D.: Thank you. I will present to you the incidents, rates, and causes of out reachment, modification, cipreth [misspelled?] care center in Abejwa. The cipreth is the most important HIV care center of Akwanda [misspelled?] network.

ACONDA is an NGU that has been funded by the FR

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[misspelled] since 2004. During the first three years of the program, 2,012 adults started at in the Cipreth care center, patient were predominantly women.

Their median CBC before initiation was 125, fair to medium [inaudible]. The median hemoglobin was 94 and their BMI was 19.5. The women first line at regimen was D4T, 3TC, and Nevirapine, Zidovudine, 3TC, and Efavirenz and D4T 3TC and Efavirenz.

The median follow-up on ART during this study period was 13-month, was still 18-month please. During the follow-up in the study, the rate of ART regimen modification was estimated at 10.5-percent person a year in patient who started Zidovudine, 3TC and Efavirenz.

27.2 person, person year in those who started D4T, 3TC, and Efavirenz, and 34 person, person year in those who started D4T, 3TC, and Neurontin.

As shown on this slide, the median delay between ART's initiation and the first regimen modification was 6.4, 12.8 and 4.8 month respectively. The drug side effect was the main reason for switch the first-line ART regimen was. However, it was not the only reason. As shown on this slide, [inaudible] was the frequent cause of liver apendiscontinuation.

And pregnancy causes of liver apendiscontinuation,

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and pregnancy a frequent cause of Efavirenz discontinuation. Unfortunately, between one and five persons of regimen modification were also due to drug stock shortage.

This slide show the rate of the [inaudible] side effect that led to us list one drug discontinuation. Overall, the rate of side effect related drug discontinuation was at 12.4 person a year, person/person years.

In patient receiving D4T continued regimen, the rate of D4T discontinuation for peripheral neuropathy was 20.5 person/person year. In patient receiving the Nevirapine continuing regimens, the rate of nevirapine discontinuation for [inaudible] side effect was 6.3 person/person year.

In patient receiving Zidovudine continuing regimen, the rate of Zidovudine discontinuation for hematological side effects was 3.5 person/person year.

Finally, the rate of the Efavirenz discontinuation for neurological side effect was only 0.1 person/person year. This data deserve the following comments.

Within the first month of Zidovudine or D4T and Efavirenz- or Nevirapine-based regimens, first of all, side effects were not the only causes of drug discontinuation as [inaudible] loses and pregnancy accounts for a significant percentage of regimen modification.

The other rate of one drug discontinuation for side

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effect was estimated at 12.4 person/person year, and the drug and causes was mainly D4T followed by Nevirapine. The discontinuation of Zidovudine and Efavirenz was very rare. Thank you for your attention.

[Applause]

FEMALE SPEAKER: Thank you very much to the three presenters. Now we are going to open up for questions and discussion about the three presentations.

We have one mic in the room and it is, or do we have two? We have two, one on the far side and one on this first aisle here. So if you could take your questions to the mic, you could get up and walk to the person with the mic, that would be terrific.

DR. SHAO [misspelled?]: Thank you very much. I am Dr. Shao from Family Health International Tanzania. My question could be answered by any of the three presenters. Some of the adverse drug reactions can be very difficult to differentiate from immune reconstitution.

I am wondering whether any steps were taken to and if they were how, to differentiate the adverse drug reactions from the immune reconstitutions?

MALE SPEAKER: Who would like, Dr. Messou?

EUGENE MESSOU, M.D.: I apologize for my English, but I want to try to respond to this question. I think that

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there is no test for general disease immune reconstitution.

But when you are in the clinic and you have people to see, I think that events, side effects can be [inaudible] by clinical staff.

And I think that is not efficient on these. Logical this year is the reason why we switched regimen because of effect even, and we know what can be immune reconstitution, because this staff medical can reflect on it, I think.

DR. SHAO: Can I add something about his differentiation? Immuno reconstitution means that there is a disease characterized by some signs, clinical signs. So in our presentation, we talk about some signs of due to some drugs like [inaudible].

So there is a big difference between immuno reconstitution and side effects. Side effects clinician, physician could know about immuno reconstitution, because immuno reconstitution appear in the beginning of treatment and is a disease, which characterized by the augmentation of CD4 count immunity.

Side effects is some signs of some signs, which is comprised the side effects of some drugs. I think you understand what I mean, even if I am not very good in English.

FEMALE SPEAKER: If you have a question, oh, we have a

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question.

MALE SPEAKER: Please, if you have a question, try and go to the microphone. Thank you.

GRACE MARISSA [misspelled?]: Thank you very much. My name is Grace Marissa, UNICEF Rwanda. My question goes to FHI and Kenya presentations. I observed that the lack of the face of children, I don't know whether it was deliberate or not. I just want to know the comparative analysis of adverse effects in children and adults, if that is within the context of the study. Thank you.

LILLIAN KOCHOLLA: Actually, at our hospital in Mbagathi, we didn't do a study on the children, mainly because we started our children's program in 2005 and currently we only have about 400 children on ART.

Out of those 400 children, we only had to switch drugs for three of them, one was due to treatment failure and two of them were due to Nevirapine rash.

GRACE MARISSA: Thank you.

FEMALE SPEAKER: My question goes to any of the...

FEMALE SPEAKER: I am sorry. Can you hold your question one, just for a moment? We are going to ask FHI to, in a sense, to respond.

DR. SHAO: Okay. What I could say is that a, when I finished my presentation I talked about risk factors. And

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our colleague from Uganda talked about risk factors, which is age. Well, he said that the age more after five years is a risk factors for the Eflorapix some side effects.

I think in our studies, we did differentiate adult and children. But I think in my experience that children support very good antiretroviral therapies than adults, but we found some unfactored toxicities due to some HIV drugs in children.

FEMALE SPEAKER: Thank you very much. Next question.

FEMALE SPEAKER: Okay. I want to ask whether in the case of the [inaudible], have they ever made a patient default from the drug, let me see, taking their ART and then stop for a while and then coming back? And if they have, what are the action they use to take on that client?

FEMALE SPEAKER: Are you directing the question to any particular speaker or the whole panel? Whole panel, okay?

LILLIAN KOCHOLLA: Let me talk about some patients for whom we have had need to switch some NRTI. And what we have done is not stopped the treatment completely, but we have stopped the NRTI and continued with NNRTI.

And this is because of the shelf life of the NRTI, so that we don't encourage resistance in those patients. So for two weeks we can stop the NRTI and continue with the NNRTI. Thank you.

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MALE SPEAKER: I have two questions. My first question goes to the lady from Mbagathi. You had a 1.4-percent treatment switch rate after three years. Now I just want to know, how are you defining treatment failure? Because that seems to be a very perfect patient population. Were you for example waiting for a patient to have clinical failure, and then do a viral load or are do that in all of your patients?

Two, the other question, I was going to look at and compared data from Rwanda and the data from Kenya. It appears like lipoatrophy was the major cause of switching for Kenya, sorry for Rwanda, sorry for Kenya, whereas neuropathy was actually the cause of treatment failure for Rwanda.

Now this seems a paradox because it takes longer to develop lipoatrophy than it does to develop neuropathy. What was your definition of neuropathy warranting changes from the two countries? Thank you very much.

LILIAN KOCHOLLA: Let me start with Mbagathi District Hospital and the question of neuropathy. We switched for neuropathy at grade two severity.

And the reason why I think we have higher incidences of lipodistrophy compared to other programs is because we have actually been running for about four years now. And that then gives us that length of period of more than 18

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months where you expect to have more lipodistrophy compared to other ADRs, sorry.

On the case of treatment failure, the reason why we have relatively low rate of treatment failure, I think, is because we have been doing viral loads for majority of our patients,

And this, we have only been able to do despite our low resource setting because of sort we have had from MSF. We were therefore able to identify these cases before they needed to be switched. Thank you.

DR. SHAO: I think the percentage of neuropathy in our settings could, is due to the period of its position. I think there is ever risk factors, which could be clarified like BMI or age or other things, which has not been in our studies.

MALE SPEAKER: Go ahead, John.

JOHN: I would like to address this comment to our Rwanda colleague. I think you are the one who made the argument for getting away from D4T as a first line regimen and going to Abacavir or Tenofovir regimens am I correct? OK.

This is a debate, and I think this will come up again tomorrow at the session that Charlie Jolt soluted to that is at 6:15 tomorrow evening. Obviously, a switch to Abacavir or Tenofovir regimen has huge cost implications.

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We know that the cost of these drugs may change. But for the numbers of people that we are talking about treating, the cost implications are huge. So I would like to ask you to defend your recommendation, and I am going to bring up a couple of points.

One is that the Ugandan data clearly showed that at 18 months, I think, 75-percent of people on a D4T regimen were still on their first-line regimens. So one could look at the cup more full than empty. And also the Koatavoir [misspelled?] data showed that the vast majority of people had no switches.

So one could look at it either way. But there are a lot of people still on the first line therapy. And secondly what data do we have to support the long term benefit of starting with Abacavir or Tenofovir regimen instead of D4T or AZT in terms of where a patient will be years down the line and I think that is an important question we need to ask. So I wonder if you might want to comment further. Thanks.

MALE SPEAKER: I am going to translate the question. All right. [Foreign translation]

EUGENE MESSOU, M.D.: In my presentation, I talk about the switching for D4T to Abacavir or Tenofovir. I think D4T is not less expensive drug to authorize. But if we consider the side effects, the cost of side effects, life threatening

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conditions and I found psychosocial disorders, I think I should prefer to begin with Abacavir or Tenofovir, because the cost of treatment of side effects, it could be high.

MALE SPEAKER: Thank you. My question goes to, first of all, I want to thank all of the presenters for a wonderful presentation. My question goes to our colleague from Koatavoir [misspelled?] whose presentation actually excited me.

Because apparently the side effects in your treatment program seems to be two, TB and pregnancy, rather than just the side effects we have been talking about.

So we have noted maybe, probably just the patients, are these patients developing TB or signs of what TB when they are on the treatment and what is your program doing about addressing better screening for TB among clients that have been in [inaudible] ART?

And secondly, what is your program doing about the reproductive health needs of women that are on ART, so that they do not end up switching from Efavirenz to Nevirapine, because they are pregnant? Thank you.

EUGENE MESSOU, M.D.: So thank you. The problem of TB is real in our [inaudible], but we think that there is not real discussion about this, because if you start our treatment you screen before starting.

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We screen people about TB, and I think our clinicians are able to do this. This clinician rejoin one clinician, one of my colleague asked me one day, I say do you think that because your TB appear in the first month of starting treatment, it means that your TB are immune reconstitution?

And I say to him that, when you have a patient in front of you and he is favor, and he cough, and very big eyes in expectoration I think that you know that, that is TB. If the diagnosis is clear, I think that TB are important in ivory coast cohorts and the diagnosis is not making with confusion. That was this, the first response I can see.

And the second question is, I mean pregnancy is not side effects. I know it. TB is not a side effect too.

But people are speaking about switching treatment and my presentation is on this. When we see our cohorts they are seeking treatment in pharmacological data, and we all people here are seeing that D4T is the only drug with to avoid our care.

But we know that when you [inaudible] a woman she, you says to her to take a progestic for a treatment, not when you give to her for example. Don't give in pregnancy. But if she come in your clinic and she is in pregnancy and she say what you do?

You seek this treatment before and after you

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discussed for the future of this [inaudible]. What is what you are doing our cohorts and I am a clinician and I do it all days.

The other commentary I can do here is not to see that when we have a patient in front of us it means that we see only the data and not the patient.

That is not the patient we have to discuss yet, but when we switch a treatment, it is because of something and I think that tuberculosis is important when one uses an NNRT treatment.

When you use Efavirenz in the first line of treatment it means that when there is pregnancy can switch it and when you use Nevirapine in your treatment it means that when there is pregnancy you can switch.

And when you are asking about switching treatment, this means that you may present it, because if you don't present it this means that you think you are some [inaudible] that is why.

I spoke about pregnancy and TB. They are not side effects, I know. Thank you.

MALE SPEAKER: And I am very glad to here that there is already some very, very good data from countries that we will be able to draw on. When we did the initial guidelines and we made the recommendations, particularly around D4T,

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there were no data out there, and it was a big issue for us trying to make decisions on what the best regimes were in the absence of key data.

I would also like then to make a second comment and that is we are trying to standardized language in this and we do urge countries and programs to talk around switching to do with failure of first line regime, and you switch and change all the drugs and ideally bring in a new class of drug and that is called switch, and it is on first line regime failure.

And so when countries talk about switch rates, we know what they mean. It is the numbers of patients, kids or adults, who go who fail first line and switch all their drugs to a second-line regimen.

I think a lot of this discussion, although the session is called switching, this is around what we would prefer people to describe as drug substitution, ideally a single drug change for toxicity, drug to drug interaction, intolerance or potential for causing damage during pregnancy.

And we really do need to differentiate those moves to alternative first-line regimens, and what we would like people to call substitution from failure and switching regimen from first- to second-line.

This is really going to be quite critical that we

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standardize these, so that when we are looking at program performance, and we can get early indicators of toxicity through the substitutions rates, we can clearly differentiate that from differences of whole regimen failure, however we define failure: chemically, neurologically or virologically. Thank you.

JOHN: I think our time is virtually up and I think that is a pretty good note to finish on. Those were helpful comments. Let me just add a couple more. Firstly, I am kind of impressed by the apparent durability of the treatments people are on despite the problems we have heard about.

As Charlie indicated, we thought this session was going to be about switching, and in fact we haven't talked at all or hardly at all about treatment failure and second line regimens.

There is a lot of international discussion about funding for second line regimens and it is interesting that in this clinical discussion it hasn't featured prominently.

Again, how to recognize treatment failure, I urge you to try and attend that session tomorrow afternoon. One would think that more laboratory monitoring would help us detect failure and help detect it early.

But it will be interesting to get some data around this sort of sensitivity and specificity of clinical

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monitoring, and I hope we will hear some data about that tomorrow.

And again, I think you have heard the comments about terminology and the importance of comparing like with like, particularly with difficult diagnostic situations like a lipoatrophy.

I would like to thank all of the speakers. The folks who spoke earlier in the afternoon, our panel members, thank you very much for this interesting discussion and thank you to the audience.

I congratulate all the speakers for sticking to time and the audience thank you so much for being so participatory and so attentive. We have about a half hour break I think now. Well deserved. Before the next session. Thank you very much and Mary, another thank you to you.

[Applause]

[END RECORDING]