

TB & HIV: Overlapping Epidemics, Overlapping Challenges
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PAPA SALIF SOW: Ladies and gentlemen, good afternoon. My name is Papa Salif Sow. I am from the Dakar University Hospital.

And welcome to this symposium, "TB and HIV Overlapping Epidemics, Overlapping Challenges," and this symposium will discuss the major issues and challenges related to the emerging and overlapping epidemics of tuberculosis and HIV and how policies and planning need to consider the overlaps.

A community and a preventative will be discussed. We will discuss personal challenges. This will be followed by a discussion on practices in case funding and identification of coinfecting persons to enable prevention strategies. The specific management issues for a person coinfecting with the two pathogens will be discussed. Comments will follow from a speaker from a high TB-incidence area and a low incidence-TB area in terms of lessons learned. Now, it is my pleasure to turn on to my co-chair, Liz, who will introduce the different speakers. So, welcome to this symposium.

[APPLAUSE]

ELIZABETH CORBETT, Ph.D.: Thanks, can you hear me? Thank you. Thank you very much. I think we have got a great lineup of speakers for this session from which we are hoping to have a good interaction from the audience, so our plan is

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to give the invited talks first and then ask the questions from the audience to guide a panel discussion.

My first speaker is Lucy Chesire from TB Action Kenya, followed by Helen Ayles, who has been working in Zambia with the ZAMSTAR Intervention Project, then Diane Havlir who is professor of medicine at UCSF and a researcher mainly based in Uganda. We then have Michel Gasana from Rwanda. He is the director of the National TB Program. Rwanda has been making great strides in rolling out joint HIV/TB services and his talk will be in French so please bear with him for that. And then we have Soumya Swaminathan from Chinai TB Research Center in India. So without wasting any more time, because we are hoping to press on to the panel discussions, I will ask Lucy to come and tell us her experiences.

[APPLAUSE]

LUCY CHELIMO CHESIRE: Good afternoon, ladies and gentlemen. I would like to thank the International AIDS Society for giving me this opportunity to share my personal experience.

I would like to start by saying that I am a woman who has lived with HIV now for 16 years and it is amazing because I lived with HIV for 10 good years and it wasn't until I actually realized that I had TB that I came so close to death. Why do I say that I came so close to death? Here I

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was, as a health care professional working in a health institution, and yet it was a mystery, trying to detect whether I had TB or not.

Now, what basically happened was despite the fact that I was actually presenting most of the signs and symptoms related to TB, my doctors were not convinced enough that I had TB and that led to delayed starting me on treatment and I ended up having TB of the chest, TB of the neck, what they refer to as TB [inaudible], and at the same time ended up having TB of the knee. It wasn't easy because I had to undergo three surgeries.

I suffered a lot and my suffering was all about delayed diagnosis and not being able to make the right decision at the right time in an era whereby we are saying that TB has basically become the killer of people living with HIV and AIDS. I am basically humbled to see at least a room that is almost filled. It shows that we are realizing that TB has become a bigger problem and we need to come together, combine our efforts in order for us to be able to save the many lives. I work in a hospital and it always breaks my heart to see a patient coming to the hospital and we are unable because they are in the AIDS state, we are totally unable to diagnose and actually comfortably say that the patient is having TB.

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I know that for sure diagnostics is a big challenge but I am looking in the coming years, what can the HIV and AIDS community do? What can the donors do? What can the civil society do to combine our efforts so that we can be able to advocate for better drugs. We know very well the drugs that are being used to TB are over 50 years old. You know very well today if somebody needed an HIV test it would take less than five minutes. But if somebody was sent to a laboratory to try and check out their sputum for TB, it doesn't take less than 24 hours. I am urging if there is anything we can do to make a difference, to save the many lives of those who are at stake of developing TB, because we all say that as long as you are living with HIV you actually have what you call latent TB.

We have got to reach a point where we can say we have diagnostics. They are actually going to be able to detect the latent TB. At the same time, there is always light at the end of the tunnel because I know currently the World Health Organization is working on some recommendations for TB diagnostics in high HIV prevalence areas and I hope that it is not going to take a long time for the publication to come out so that we can certainly actually sit down in our TB/HIV clinics and say that we are able to provide the care for our TB/HIV coinfecting patients.

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Just in case, for those who don't really know the seriousness of TB/HIV coinfection, out of the 40 million HIV infections in the world, 14 million people are coinfecting with HIV and TB. It breaks my heart to see people die from TB, a disease that is curable, a disease that is preventable, and for me, I always say we need to do something. We have what you call the collaborative activities whereby at least for the last three or five years clinics are being encouraged, HIV programs, TB programs are being encouraged to work together so that as you walk into a TB clinic you can be offered testing for HIV. As you walk into an HIV clinic, I am comfortable. When I go for my monthly check-ups, they are able to try to see whether I have TB or not, or even they can put me on prophylaxis treatment for TB and that is really good news.

We must stop the suffering that comes from HIV coinfection and it is going to take each and everybody in this room to realize they have a responsibility to make a difference for the many people who could easily die from a curable disease considering that I have lived with HIV for over ten years and almost came to my death bed because of having TB. I will call out to you all, let's make a difference for I believe every life has an equal worth. Nobody needs to die. Together, we can make a difference. Thank you.

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[APPLAUSE]

ELIZABETH CORBETT, Ph.D.: Thank you very much, Lucy. I think that really sets the tone for where we are coming from, a huge burden of suffering and as you said on the face of it, unnecessary suffering. Our next speaker is Helen, so Helen. if I can ask you to go ahead.

HELEN AYLES: Do we have the slides? Good afternoon. My name is Helen Ayles. I come from the Zambia AIDS Related Tuberculosis Project, which is a project that has been looking at the overlapping epidemics of TB and HIV for the last 15 years and I would like to talk about TB case finding and TB prevention in HIV infected populations.

I'd just like to run over a little bit of the epidemiology of these overlapping epidemics. This cartoon shows one person who is suffering from tuberculosis. They are infectious. They are coughing up microbacteria in tuberculosis and from epidemiology we know that on average they infect 20 other people in their community with tuberculosis. Now for most of these people, that is not a problem, but for about 10-percent in their lifetime, they will go on to develop active tuberculosis. And on average, one of those will be an infectious case with smear positive disease and one will be a less infectious or non-infectious case with smear negative or extra pulmonary disease. And so

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one infectious case generates one infectious case and we have stability.

If you put HIV into the equation and if you put in an HIV prevalence in the population of about 10-percent, which is quite moderate from the part of the world where I come from, the situation changes. The same infectious case still infects 20 people in the community and for the 18 HIV negative individuals, they still have the same risk, 10-percent, in their lifetime of going on to develop tuberculosis. But for the individuals with HIV who have become infected with tuberculosis, they have a much greater risk of progressing to active disease. And so if we say on average, we get 0.8 of a case then and even allowing for the fact that more of those will have the less infectious versions of tuberculosis, the smear negative or the extra pulmonary disease, we still end up generating 1.2 infectious cases so one case has now generated 1.2 cases and so we have an epidemic on our hands.

Just to demonstrate that this isn't just a cartoon, this is the situation from Zambia where I come from and you can see that TB incidence was stable in Zambia at a rate of about 100 per 100,000 population per year all the way until the mid-'80s, and then suddenly tuberculosis took off. This slide only goes up to 1996, but now TB incidence is over 500

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per 100,000 of the population per year, so a fivefold increase, and this is purely due to HIV.

Zambia is not alone. This slide shows the estimated tuberculosis incidence for countries plotted against the estimated adult HIV seroprevalence and I think you can see that actually this is a pretty good correlation, that no country with a high HIV seroprevalence is managing to control its tuberculosis.

So what can we do? This is the same cartoon. Well, I think there are three main places we could act. We can reduce the transmission. We can try to reduce the number of people that each infectious case infects. We could reduce the reactivation in HIV positive individuals so that they don't go on and develop tuberculosis once they are infected and we could reduce the prevalence of HIV.

Now, what I've said really is from a TB perspective, but if we think about it from an HIV community perspective, how does TB impact on your daily life? People living with HIV are continuing to be infected with TB in high prevalence settings every day and are continuing to die from tuberculosis. Tuberculosis is risking your antiretroviral therapy programs because people are still developing tuberculosis, even when they are on antiretroviral therapy. We know that there were many presentations here yesterday, I think, on tuberculosis so I hope some of you were at those

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sessions, where people were reporting rates of up to 15-percent of patients starting antiretroviral therapy developing tuberculosis within the first year after starting that therapy. And although then subsequently the rates decline, the rates of TB in this population are still about five times that in the HIV uninfected population.

So what can we do? We need to find more cases of active TB and treat them earlier and then we need to reduce the reactivation of the latent TB in those individuals who do not yet have active TB and both of these strategies will prevent TB. TB preventive therapy is a well proven intervention for people living with HIV. [Inaudible] review of 11 randomized trials in HIV positive individuals showed a significant reduction in tuberculosis in HIV-positive individuals who are taking preventive therapy. National and international policies have existed for over 10 years but the uptake has been very poor in the high burden countries.

Why has the uptake of this intervention been poor? Well, I think it is being directed really at the TB control program who really work on a very public health approach and for them the most public health beneficial intervention is to find cases of active TB and treat them rather than looking for cases of latent TB to prevent developing into active TB. I think there is also reluctance because it is quite difficult to screen who should be getting TB preventive

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therapy and also the fact is that the drugs that we can use to prevent TB are still the only drugs we have to treat it.

So, what can we do? Well, I think the most important thing is that we can screen all HIV-infected individuals for TB. I was pleased to hear that Lucy says that she is screened when she goes for her check-ups. By screening, we will find people with active tuberculosis who we can treat and by finding them earlier and treating them earlier we can achieve better TB outcomes. That screening would also identify people who could benefit from TB preventive therapy.

What are the yields? Well, screening for active TB in different settings, BCT centers, PMTCT programs, HIV clinics have shown a yield of between 0- and 6-percent, depending on where they are, of people living with HIV who have been screened who had their TB detected through this route, and how many people could we find who could benefit from preventive therapy? Well, anywhere between 10- and 50-percent. Then the questions are how to screen, when to screen, and where to screen, and I think we also have to consider whether we really need to diagnose latent TB in the high prevalence areas.

So, how to screen for TB, various ways have been posed and the ways that we have screened for TB are also the ways that can be used to exclude active TB, which is necessary before considering treatment of latent TB infection

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and then we have some tests as well to screen for latent TB and I am going to briefly go through this list.

So, the symptomatic screen is the most commonly done. It is very easy. It is very simple. It is just a few questions. Screens that different people have used vary but most include the same symptoms, the cough, fever, night sweats and weight loss, and this screen is pretty sensitive. It picks up most people who have active TB. The problem is it also picks up many people who don't have TB, but it is a good entry point into a screening process that if somebody is symptomatic you need to go on and do more. Chest X-rays have been used quite extensively. The problem is they are not always straight forward as this chest X-ray. This is a very classical chest X-ray of tuberculosis found in a community prevalence survey that we have just been conducting in Zambia but many are very non-specific and repeated studies have found that in people with culture proven tuberculosis can have normal chest X-rays, so they are difficult to interpret and for that reason they also have a lower sensitivity than a symptom screen, although they may improve specificity. They are not very available in low-income settings and in high-income settings, lower-prevalence settings, they have been demonstrated on several occasions not to be cost effective. And people don't recommend routine regular screening with chest X-rays but they can be used after a symptoms screen.

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Sputum examination, which is really I think the bug bear of all of us who work in tuberculosis, because this is our main means of diagnosis. Sputum smear is cheap and readily available but has a poor sensitivity in practice, although that can be improved by different techniques such as fluorescent microscopy, but it is very specific. Sputum culture is more expensive and much less available, still slow and there are newer methods, like the culture, which has well been used for a long time, I know, in high-income countries, which is just being tried in lower income countries, although it still has its challenges with high contamination rates and also picking up other microbacteria which can delay the results getting out to individuals.

We desperately need new diagnostics for TB and I know that there are many people working on this, the Find Group in particular are looking at newer techniques include nucleic acid technologies, phage technologies, and also looking for the holy grail, the point-of-contact dipstick test that HIV communities have had for a long time and we are still waiting for in tuberculosis.

I think the screening when and where is easy, it should be always on every visit on diagnosis, in VCT centers, PMTCT settings, and as I say if you use a symptom screen that is really quite easily done and feasible and affordable. So if we go back to this cartoon, you screen all infected

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individuals for TB and you can detect those with active disease and exclude those you would think have no TB but there is always a grey area of unknowns. You can't say that this person definitely has TB and you can't really 100-percent say they don't have TB. Now in the BCT and PMTCT setting, this group is a fairly small group, but if you are waiting for ART and HIV clinical settings, this group becomes very large. It is quite difficult to rule in or rule out active TB. When you have ruled out active TB, then you can consider whether you should give this person treatment for latent tuberculosis infection preventive therapy.

How to diagnose TB infection? Well, our gold standard is a test that is over 100 years old, the tuberculin skin that involves injecting purified protein derivative into the skin. It is cheap but has its problems. It is very easy - there are false positives. I just showed these pictures which are from schoolchildren but showing a very clean curve in a group of South African schoolchildren. And this is our Zambian data showing a big bunch of people who probably aren't infected with TB but with other microbacteria so the test is not specific and more importantly in the HIV population is not sensitive.

Even in smear-positive TB patients in Zambia when we do TSTs, we only have a positivity rate of between 20- and 30-percent, and that is well known in other settings as well.

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The delayed hypersensitivity reaction is lost quite early in HIV.

We do have some new tests in this field which are the interferon gamma release assays in vitro tests which use antigens from the region of difference of MTB. These definitely have a higher specificity than TST for tuberculosis and we believe they have a better sensitivity, especially in HIV. We did some early work on this in Zambia which seemed to show that but again, even in this conference, there have been some reports showing that probably at very low CD4 counts, the sensitivity is lower. These tests, however, are expensive and do need laboratory facilities with electricity and running water and so are of limited use at the moment in many high burden countries.

So I come back to my point. Do we need to diagnose latent TB in high prevalence countries? We definitely must exclude active tuberculosis but then can we just assume that HIV infected individuals have probably been exposed and infected and just prevent TB anyway? Certainly, that is the model that Botswana has used. It is one of the only countries that have rolled out preventive therapy on a large scale. They exclude active TB and then treat with preventive therapy. Preventive therapy that is currently in use is isoniazid. The duration is still under debate. The current

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recommendations are between six and 12 months, depending on which bit of the world you come from.

The question is, is this sufficient in high TB-transmission areas? This graph shows a trial, again from Zambia, these are years down at the bottom showing that both isoniazid alone and rifampicin and procinonide protect quite well, this is the survival curve against TB, for about three years after a six-month course but then the benefit wanes. We need trials to see how long we really need to give this for. And I know that there is a trial under way at present, again in Botswana, looking at this issue, but it will be quite while before we have the answer to that.

We also don't know the value of isoniazid with antiretroviral therapy. As I said right at the beginning, we know the people on antiretroviral therapy are still getting TB so would it be beneficial to add isoniazid preventive therapy? Of course, there are issues here about side effects, drug interactions, particularly hepatic toxicity and peripheral neuropathy with the first-line regimens currently being used in high-prevalence countries. And, again, there are trials under way looking at whether this would give additional benefit and whether these potential drug interactions would be significant or not.

So in summary, I think we need to screen all HIV-infected populations for TB. We need to treat active TB. TB

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is curable. I think in high-income, low TB-prevalence settings, it is important to test for latent TB. You have the resources, you have the tests. I think the new interferon gamma release tests are much better in our population and then you can target your TB preventive therapy to those who need it most and where it is most cost effective. I think in low-income, high TB-prevalence settings, we are only going to be able to exclude active TB or try. I don't think testing for latent TB is going to be feasible and I think therefore we should use TB preventive therapy.

Where should we use it? I think it is difficult to exclude active TB and until we have got better diagnostics, or we have got new drugs so that we can reserve one drug solely for preventive therapy, we are going to have to choose our group quite carefully. I believe it is easier to exclude active TB in the early HIV population, asymptomatic individuals presenting to VCT and particularly PMTCT, individuals who come into HIV care early before they need antiretroviral therapy who could benefit. And I would like to thank my team in Zambia who have done all the work and advised me. Thank you very much.

[APPLAUSE]

ELIZABETH CORBETT, Ph.D.: Thank you very much, Helen. That was a great talk and I hope very stimulating. Lots of questions come to my mind anyway. And Diane, we are

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now ready for your discussion on the challenges in treatment of coinfecting patients.

DIANE HAVLIR: Thanks to the organizers for inviting me to speak today. I am going to be talking about four challenges related to HIV-infected individuals with tuberculosis. These include when to start antiretroviral therapy, what antiretroviral therapy to start, TB immune reconstitutions, ART treatment failure, and second line antiretroviral therapy during TB treatment. I chose these because whether you are in efficacy, policy, industry, or the clinical front. I hope one, if not all, of these issues will resonate with you.

So, our first question of when to start antiretroviral therapy in individuals who have a new tuberculosis and HIV diagnosis is a very practical one and it is a very common one. Many studies have indicated that many people find out about their HIV diagnosis at TB clinics. A very nice recent report from Zambia, Dr. Nun discussed this in his talk on Sunday, but the bottom line is that TB is going to be a common entry point for HIV diagnosis.

Unlike many other opportunistic infections, TB occurs over a broad range of CD4 cell counts. Last year, at the IS meeting in Argentina, Fabio Escano and colleagues presented a very interesting report that suggested that perhaps the CD4 cell count was lower in more patients than we had originally

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thought and this is particularly important because there are extraordinarily high rates of mortality associated with TB and low CD4 cell counts. I think one of the tragic ironies of this disease, which we need to prevent from happening, is that TB can be one of the most common entry and exit points, so one of the ways to address this is through antiretroviral therapy and just very simply stated, an individual who is HIV infected who has tuberculosis, we need to ask ourselves is antiretroviral therapy indicated and if it is, when should it be started?

Well, we use antiretroviral therapy in individuals who are among highest risk of HIV disease related morbidity and mortality so certainly individuals who have low CD4 cell counts, those with WHO stage 4 disease or AIDS diseases apart from tuberculosis and of course disseminated TB is a WHO stage 4 disease. We are not really sure about higher CD4 thresholds over 350, and there is certainly a healthy discourse right now of over 250 CD4 cell counts. This is really quite a complicated question because in the setting of TB and other opportunistic infections, CD4 cell counts may be transiently depressed. CD4 cell count testing might not be available at all and, of course, as we hear repeatedly, the diagnosis of TB can be extremely difficult.

So, if we do decide that antiretroviral therapy is indicated, when should it be started? So, in a patient that

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has tuberculosis and HIV diagnosis is made and CD4 cell counts are low, should we start it at exactly the same time that we initiate TB treatment? Should we wait two months until the TB therapy is simplified? Or should we wait until TB therapy is completely completed?

What are the potential benefits and risks of these two strategies? The benefits of starting antiretroviral therapy early include reduced morbidity, reduced mortality, and theoretically although not proven, improved TB outcomes but this is countered by some risks that need to be carefully examined. When we give both these medications together, we certainly see increased toxicity to TB and antiretroviral therapy. In addition to the morbidity it creates for patients, one of the consequences of this are therapy interruptions and we certainly know from the HIV perspective that repeated therapy interruptions puts a patient at risk for drug resistance and second-line regimens just are in short supply right now so this can have serious consequences down the line. In the same way, there are drug interactions between HIV and TB medications. Most affect the HIV medications where levels can be lower and once again putting a patient at jeopardy of developing HIV drug resistance. Pill burden is, of course, higher and then immune reconstitutions or paradoxical reactions transient worsening of tuberculosis after starting antiretroviral therapy, which

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actually can be very severe reviewed beautifully in a paper by Steve Lawn recently can require steroids.

So, most of the observational studies have suggested that earlier is better, but while observational studies are important, they are susceptible to great bias. And there are still equipoise in the field about the optimal time to start antiretroviral therapy in patients who are diagnosed with tuberculosis and to this end, these are three large randomized studies collectively with over 2,000 patients that have either started or just about to start, they are going to be addressing this question, one in Cambodia, one in about 20 sites around the world, and another in South Africa. So, it will take some time to answer these questions.

In the meantime, the new 2006 WHO guidelines recommend the following. Individuals with less than 200 CD4 cell counts, antiretroviral therapy is of course recommended and TB started between two and eight weeks for slightly higher CD4 cell count it is also recommended, but after eight weeks, and then when CD4 cell count is not available, it is still recommended somewhere early on and there are many caveats that are listed in the table here that are available on the web.

So, what antiretroviral therapy is optimally used in patients with tuberculosis? Here are the issues that we have to deal with: Drug interactions, toxicity and

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teratogenicity. The biggest problem is with rifampin. Rifampin is a potent inducer of CYP3A4 in the hepatic P450 system. This is how our HIV NNRTI's and protease inhibitors are metabolized and hence, when you give these compounds together we get reductions in our NNRTI's and our protease inhibitors. But rifampin is an invaluable drug in the treatment of tuberculosis and it has superior outcome.

And a very beautiful review by our moderator, Dr. Corbett at *Lancet*, she makes the point that we should be striving to have full dose rifampin regimens in our TB regimens so this poses a problem. So let me share with you some of the data that are available about rifampin interactions with our first-line HIV medications, specific NNRTI's. So the exposure to efavirenz and Nevirapine in a wide array of studies are reduced somewhere in the range of 20- to 40-percent when given with rifampin. Now, with this reduction, investigators have gone on to say well what if we increase the dose of efavirenz or what if we increase the dose of Nevirapine, can we overcome this reduction? And in fact, in the pharmacologic drug interaction studies and Dr. Slomi Nathan's group just recently published a study about Nevirapine, it can be done.

However, very important observation that has been made over the last probably two to three years, there is incredible interpatient variability of NNRTI drug levels and

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it appears to be due to genetic determinants of metabolism. And, in fact, countries have appropriately forged ahead and given rifampin-based regimens with these non-nucleosides, both of them, either Novaripine or efavirenz, and the clinical outcome data, at least that I have seen to date, don't support dose adjustment of either efavirenz or Novaripine. In fact, there was one study which showed some toxicity when patients were given the higher doses of efavirenz.

There was a nice report recently published in *AIDS*, which is a randomized trial looking at efavirenz 600 mg vs. 800 mg in a Thai population and overall, the drug levels looked pretty similar. There were a slightly higher percentage of individuals who had the lower dose of efavirenz when given with rifampin but all in all the bottom line for this study was that the clinical outcomes were the same. This table summarizes several studies which have compared the outcomes to antiretroviral therapy between patients with tuberculosis receiving rifampin to those who don't have tuberculosis and in general the CD4 and HIV RNA responses have been similar. Now once again, these are relatively short-term outcomes. We are concerned about resistance down the line but I think these are extremely important and informative data.

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So, in addition to drug interactions, we have drug toxicity. Certainly the clinicians in the room are all familiar with hepatitis and rash are probably two of the most challenging that we have to deal with, with our non-nucleosides, particularly Novaripine and we can see these toxicities also with our anti-tuberculosis medications. Hematologic toxicities, thrombocytopenia is one that we have to grapple with and frankly all these medications can give gastrointestinal toxicity. Neuropathy and severe neuropathy can occur certainly with T14 to a lesser extent than CTV and this is an overlapping toxicity with our TB medicines, and really to further complicate issues, all of our patients should be on trimethadione sulfa, Bactrim or Septrin, whatever you refer to, but this particular medication also has these toxicities.

So this is extremely challenging for clinicians and the message is that we shouldn't do it and it can't be done but we just need to plan our program so we give adequate support to the people who are caring for the patients because many clinical management questions arise in this setting. Certainly at least half the individuals who will have HIV and TB are women and we have the challenge of efavirenz in this setting. As we all know, efavirenz is contraindicated in the first trimester in women and where adequate contraception cannot be ensured due to it is teratogenicity. Novaripine is

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an alternative but we need to do careful monitoring, particularly in women with high CD4 cell counts and of course we may be in the situation where we don't even have access to CD4 cell counts.

In this particular setting, certain triple NRTI regimens are an alternative. The ones are listed here which I think should probably be the front line agents in this setting. This is an active research question. This is a regimen also that is being endorsed as an alternative in the pediatric population so right now, based on the available data, the preferred regimen to give in patients with tuberculosis who are receiving rifampin is efavirenz and 2NRTI's. With increasing ability of co-formulated medications, this would be terrific that we could actually have a once a day HIV regimen that could be given with our TB regimens in a DOT setting and I know many groups have really shown nice data by really the beneficial effects of taking this approach. Novaripine is an alternate regimen. I think data are, I feel cautious but increasing reassuring, of course we need to carefully look at any evidence of hepatotoxicity and as I mentioned, triple NRTI's and abacavir or tenofovir based regimen would be an alternative.

So, one of the emerging clinical questions is in patients who have started on antiretroviral therapy, when they develop tuberculosis, whether this is an indication of

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HIV treatment failure, and there was a session yesterday which provided some interesting data on that which I will refer to and let me just show you this schematically so we have a patient who starts an antiretroviral therapy and then at some time, at six months, at a year, he develops tuberculosis and we know in fact that this is really quite a common event. Let me give you a very specific scenario, a 23 year old female with a baseline CD4 cell count of 35 starts antiretroviral therapy, develops pulmonary TB at 12 months, her CD4 cell count is 52, she says she is adherent to antiretroviral therapy, does TB in this setting indicate antiretroviral treatment failure?

On the one hand, we know TB occurs after starting antiretroviral therapy. On the other hand, her CD4 cell counts are still quite low. She is at risk for other immune events. So, with TB early after antiretroviral initiation, what can it be due to? Undiagnosed tuberculosis, activation of latent tuberculosis, transmitted tuberculosis, or immune reconstitution? And in this setting, immune reconstitution refers to the situation where subclinical tuberculosis, when an individual becomes clinically manifest, when he or she is given antiretroviral therapy in at least an amount in inflammatory response, there are ways we can try to distinguish these two, but in these four different ways. But

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most of the studies to date have lumped all these categories together.

There was a very nice study just recently published in *AIDS* from the MSF group with over 3,000 patients and they looked at TB cases after antiretroviral therapy initiation and what you can see is that across the board that these rates are quite high, probably lower than the prevalence rates in the country, and slightly higher with pulmonary vs. extra pulmonary TB. I believe in this report about 50-percent of the cases occurred within the first three months of antiretroviral therapy but importantly these cases are occurring out one, two and three years, but there was a theory, a nice and important study presented yesterday by Andrew Cambuga from Dr. Moses Kanya Group from the IDI. And what they did is they looked at a cohort of patients who were starting antiretroviral therapy who developed tuberculosis after starting and their incidence rate was similar to what I had shown you from the MSF data. But I think what this study brought to bear, which I think is a very important question, as they looked at HIV RNA levels, and what they found was HIV RNA levels were undetectable in 14 of the cases so what this means is they were doing totally fine so we can't immediately attribute treatment failure to tuberculosis.

So, in summary, tuberculosis is an indicator of antiretroviral treatment failure. Early TB cases within the

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first year of antiretroviral therapy are common. Most cases, probably represent existing TB disease and not antiretroviral treatment failure. I think the goal should be a seamless transition to TB regimen with a compatible antiretroviral treatment regimen, and certainly improved diagnostics, access to HIV RNA would greatly assist in management. Even a qualitative assay that we could use for HIV RNA would ensure that patients who really need to switch are able to and those who don't need to don't switch prematurely.

So my final challenge here, second-line antiretroviral therapy and tuberculosis, and here we have to deal with drug interactions between rifampin and the protease inhibitors, drug toxicity, and drug cost. Rifampin cannot be given with un-boosted protease inhibitors because the levels of the protease inhibitors are reduced by 70-percent. Our cornerstone of second-line therapy in HIV and the rollout is a boosted protease inhibitor but when this is given with rifampin, we still have to deal with issues of drug interactions and toxicity, not to mention the other cost and storage issues.

This slide summarizes some data that we have about lopinavir, ritonavir, studies which have been done with rifampin. Ritonavir, the dose of ritonavir has to be doubled in the study to compensate for the hepatic induction effects of rifampin, so in this PK study, although reasonable levels

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of lopinavir could be achieved, there was significant GI toxicity and lipid [inaudible] and elevations in transaminases. Likewise, in the study of boosted saquinavir given with rifampin in healthy volunteers, there were high rates of hepatitis and transaminases, 20 times the upper limit of normal, resulting in a black box warning.

These studies are just cautionary and tell us what we need to look for when we look at this question and research some of its settings because certainly the toxicity we see may not apply but I think we need to be aware of it and be cautious. Rifabutin is a semi-synthetic derivator of rifampin that is a less potent inducer P450 and can be administered with protease inhibitors so what are the current limitations with rifabutin? The cost of four days of rifabutin is approximately the cost of an entire rifampin regimen. It has its toxicities and there are some fairly complicated dose adjustments that need to be made with antiretroviral regimens but certainly our advocacy, all of us in our advocacy role should not dismiss this as a possibility.

I would say in the meantime, while we are awaiting results of studies looking at boosted PI's with rifampin, if there is not an urgency to switch to a second-line regimen, we wait. We treat TB. We get it under control. And if there is an urgency, we use a boosted PI regimen with a very

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careful monitoring. Well, you will hear a lot about new HIV drugs at this meeting. The future of TB drugs is looking much more optimistic and once again this has been reviewed in a couple of the TB sessions at this meeting already. I think some of the exciting things are there are some candidates that look like they may be able to shorten TB therapy and then perhaps have less overlapping toxicity and drug interactions than our current menu of drugs.

So, in conclusion, there are major challenges in treating HIV/TB patients that define an urgent research agenda, first-line ART, second-line ART, and treatment strategies. Research is key to move from opinion to evidence based approaches to the treatment of TB and HIV.

But in the meantime, treatment of HIV and TB in patients must proceed without delay with the best available data while we are awaiting the results of research and certainly we need to remind ourselves over and over again that integration of TB and HIV care is and will be critical for success of treatment of both of these diseases.

I was asked to talk about the challenges of TB and HIV and as an optimist, I view challenges as opportunities and we have in front of us the opportunity to improve outcomes for both TB and HIV and that is our challenge for all of us here in the room today. I would like to thank and acknowledge many of the collaborators I have had the

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privilege of working with over the years and once again, I picked just a couple of the challenges. I hope during the discussion part of this that individuals working in this field will raise additional challenges such as MDR TB and how this affects the epidemic. Thank you.

[APPLAUSE]

PAPA SALIF SOW: Thank you, Diane, for [inaudible] TB and HIV. Now it is my pleasure to introduce our next speaker, Dr. Michel Gasana, who is the TB manager program in Rwanda, a country with a high TB incidence. Dr. Gasana, you have the floor.

MICHEL GASANA: [IN FRENCH]

[APPLAUSE]

PAPA SALIF SOW: Thank you very much, Dr. Gasana, for giving us an example from Rwanda. Now, our last speaker is from India, Dr. Soumya Swaminathan, who will give us the example from a low-TB incidence country, India. Dr. Swaminathan, you have the floor.

SOUMYA SWAMINATHAN: Good afternoon, and I would like to thank the organizers of this symposium and the IES for giving me this opportunity to share experiences from a high TB-prevalent but a low HIV-prevalent country that that is India. You can see on this map, India and China were the two countries that had more than 1 million TB patients last year. India, in fact, reported 1.8 million TB cases last year.

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This has been more or less constant. For many years, we have a latent TB prevalence rate of about 50-percent in our population.

The number of HIV infections, as you might have heard, 5.2 million, is second in the world next to South Africa, but the adult HIV prevalence in our population is 0.9-percent because of course we are a population of 1.1 billion people. Forty-percent of our infections are in women, 57-percent are in rural areas. Most of [inaudible] heterosexual transmission and 95 districts are now being identified as high prevalence, that is having an anti-natal prevalence of over 1-percent.

The variation in HIV prevalence is quite high and you can see from this map that the darker areas are the southern states, the four southern states, [inaudible] and the two northeastern states of [inaudible] are the ones with the higher HIV prevalence. Even amongst those states, there is a lot of geographic and we have prevalences ranging from 0.1-percent to up to 4- or 5-percent in pregnant women.

[Inaudible] the national TB control program, I implemented it in 1997 and earlier this year we covered the entire population by dots. We use a twice-weekly regimen, which is fully supervised and every month we are putting more than 100,000 TB patients on treatment. The case detection rate is around 70-percent and our treatment success rate has been

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over 85-percent for the last several years, so we have a well-functioning, well-established TB control program.

This paper published last year looked at the impact of HIV alone. As of the current prevalence, the dots are NTCP dots and both on TB prevalence, incidence, and mortality in India. And basically what this shows it that the RNTCP dots, which is the middle column, working by itself would have reduced TB prevalence, incidence and mortality rates tremendously by 2015. Because of the impact of HIV, the rates are not going to go down to that extent and taking just the four southern states, the mortality rate in particular which is the low most column, doesn't really go down to what is expected by the millennium development goals by 2015.

So what has the government done? We had a TB/HIV action plan launched in 2001 which has now been expanded to cover almost 600 million people. It includes training at all levels of staff, service delivery linkages, and monitoring. There is a TB/HIV coordination committee that is chaired at the national level by the heads of the TB and AIDS control programs and this goes down to the district level. We have set up a periodic HIV surveillance among TB patients, Foresights, done this year. It is going to increase to 20 sites in 2006. There are lots of NGOs that are working in India. Those enrolled in the RNTCP are going to be trained to provide for HIV diagnosis and care and similarly the NGOs

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that work with HIV affected populations will be trained to be used for TB counseling and testing.

Now this survey done last year was very selective. It was done only in four HIV high prevalence sites in the four southern states and you can see that HIV positivity among TB patients range from 4.3- to 16-percent, which is actually quite high. We also looked at validating the ratio of HIV prevalence among TB patients to the ANC prevalence and it looks pretty consistent. The ratio is about five times in TB patients as in ANC so possibly that could be used as a surrogate marker.

My center also did a survey among TB, 3,500 TB patients in four different districts in [Inaudible] and again found a wide variation from 1.5- to 10-percent. We asked these 3,000 TB patients if they would be willing to get HIV tested and attend a voluntary counseling and testing center because we worried about whether they would be some kind of stigma attached to HIV testing in TB clinics. The majority of them, more than three-quarters, were willing to get HIV tested. Some of the reasons for not wanting to go to the ECTC was a perception of not having any risk behavior, 29-percent, and these were primarily women. And as you know the main risk factor for women to get HIV in India is marriage, so obviously they don't consider themselves to be at risk. Twenty-four-percent said they were too old, didn't think they

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could have HIV, and a few said that they had already had it done.

Another important factor was the physical proximity of the counseling and testing center and also availability and attitude of counselors. We have crossed referrals so these are patients or clients who from VCTC centers were screened for symptoms by the counselor and then referred for TB screening. Again, this is a pilot report in the first quarter from the six high-prevalence states and you can see that of the patients referred for TB screening, almost a quarter of them turned out to have TB. Of course, they were mostly negative cases amongst the HIV-positive, but what is interesting here is that we talk about TB clinics as an entry point for HIV care and support, and here is a VCTC which looks like it can be a very good entry point for TB diagnosis active case finding, even amongst HIV negative clients, so that is good news for the TB program.

TB and HIV generally come from two different cultures. The TB program is a public health approach, has standardized diagnosis and treatment algorithms, simple regimens and the services are completely decentralized down to the primary health care level. Whereas HIV still has a more individual approach. There are rapid paradigm treatment changes, it is lifelong treatment and antiretroviral treatment clinics are still very hospital centric so these

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are the challenges that we face. The TB program is completely decentralized. The voluntary counseling and testing center at the moment are available at the district level but we do plan to go down to the primary health care level as far as possible.

At the moment, we have 54 antiretroviral treatment centers in India located mainly in the high-prevalence states, but by the end of this year we should have 100 centers. An estimated 35,000 people are on treatment now but this should go up to 100,000 quite quickly. The challenges for people who are getting both TB and HIV care are that they have to travel long distances to get their antiretroviral treatment and there are some difficulties in coordinating between managing their TB regimens and their ART regimens and of the same monitoring adherence and adverse effects.

How better can we integrate? We are thinking about training existing staff at the primary health center levels as counselors so that we could do rapid tests right then and there. We could use existing VCTC's as centers for sputum collection and the same lab technicians would have to do both.

And before I end, I just want to say one word about the nutrition status because we all talk about TB treatment and HIV treatment and we often forget that behind all that there is a person who is very, very malnourished and is

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probably not getting three square meals in a day. And here we looked at the impact of having TB on the nutritional status of HIV-positive people compared to HIV-negative controls from the same socioeconomic background. And we can see that there is a gradation, asymptomatic HIV-positive people are more malnourished than their HIV-negative controls and once they have TB, well, they are much, much more severely malnourished. We also know that the outcome of TB treatment is linked to nutritional status.

This is a study done in a largely HIV-negative population and we can see that the TB mortality case fatality rates was four times more in those who started off with a body weight of less than 35 kg compared to those who had a body weight of more than 45 kg. And so we have to remember that we have to take the patient as a whole and not just treat their HIV and TB but make sure that their other needs are met as well.

I am very grateful to the heads of both the TB and the AIDS control programs in India as well as to my collaborators and HIV positive participants of our studies. Thank you.

[APPLAUSE]

PAPA SALIF SOW: Thank you very much for that, lots to learn from India about HIV prevalence and high TB

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incidence. Now I am going to turn onto Liz, who will lead the discussion from the floor.

ELIZABETH CORBETT, PhD: Thank you very much. I am just quickly looking through these AIDS question cards for any common themes. I don't think I am going to. Let me just pass the ones that belong to [inaudible]. That's great. I think we have heard some very interesting talks as well as these cards. [Mumbles]

PAPA SALIF SOW: Yes, some questions from the floor. [Inaudible] Lucy.

ELIZABETH CORBETT, Ph.D.: Okay, Lucy, can you have a look at your questions on your cards and please tell us your response to that? And I also have a question for you, actually. I am just interested in how has your perception of being a health care worker and exposed to TB?

LUCY CHELIMO CHESIRE: She asked a very interesting question but before I go to that, I was going to request could Dr. [Inaudible] be in our audience? Because he has asked a question about how can HIV services be linked to TB services in resource-limited settings? I was just thinking of giving him an opportunity to share our Kenyan experience since Kenya is one of the countries that actually is in a very resource limited setting. Could he be in the audience? Okay, thanks. Are you going to answer?

ELIZABETH CORBETT, Ph.D.: He will do it.

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MALE SPEAKER: Thank you very much, Lucy. I thought I could not be able to answer that. It is not easy to link TB and HIV services in a limited resource setting because there are so many challenges. In Kenya, what we have found is that the biggest challenge is human resources and getting the necessary staff. For example, to offer both diagnostic and treatment services in the TB clinics and also in the HIV sites.

The other thing is the decentralization that is in place. The TB services are slightly more decentralized than the HIV services and this offers a unique challenge because when a patient is diagnosed to have HIV in a TB clinic and this is in a rural setting where we do not have HIV services, it offers unique challenges for the patients to move from that point to seek care in a place where there are HIV services.

The other thing, of course, is infrastructure. In most places, the offering of testing of TB patients for HIV are so far a unique challenge because you need to offer counseling services and you need extra room. This is offering also unique challenges. Thank you very much.

ELIZABETH CORBETT, Ph.D.: Thank you.

[APPLAUSE]

LUCY CHELIMO CHESIRE: I think one of the greatest challenges that I basically faced in terms of being a health

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care worker and having developed TB, I wouldn't really say per se that this could have been [inaudible] infection at any one point in time because by the time I actually ended up getting TB I was not on duty. And I believe it was just an opportunity whereby because I was immune-compromised, whereby now the latent TB actually ended up developing into active TB.

But it brings another question whereby we are looking at today the kind of stigma that is greatest contributed by the health care workers. You look at scenarios whereby you could be walking in a TB/HIV clinic or in a hospital within the HIV program, a nurse walks in and she say, I believe - She is addressing HIV-positive patients and she is saying I believe all of you actually know the reason why you are here. How would you feel?

It is not easy but we must continue with the determination to fight stigma and I must say that even in relation to stigma that comes because of being or having TB, many a time it is not easy but through psychosocial support and the programs that have been established within HIV programs, many people are getting to know that we can win this fight and the battle starts from the individual and if they can make a difference in their own lives, we can be able to win the fight.

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ELIZABETH CORBETT, PhD: Thank you. I'll now ask Helen Ayles to answer her questions.

HELEN AYLES: Thank you. I've got a couple of questions here. One is really from Ethiopia which is talking about the challenges of implementing isoniazid prophylaxis and the problems with ruling out active TB.

And as I've said, this is a major barrier to the implementation of isoniazid because we are worried that if we don't adequately rule out active TB that we will be starting somebody who might have TB on a single drug and induce resistance to that drug and since that drug is commonly isoniazid, which is one of the mainstays of our TB treatment, we are all very worried about inducing resistance to isoniazid. And really that is why I have come more and more to believe that it is incredibly difficult to rule out active TB in somebody with late stage HIV disease who is multiply symptomatic. The symptom screen doesn't rule out active TB adequately in that population. X-rays aren't of any use. The diagnostics we have got are not adequate enough and so I think it is incredibly difficult and I think in late stage HIV, probably at the moment with the diagnostics we've got, it is impossible.

And so that is why I believe we should focus on early HIV disease, because I think in early HIV disease it is much more simple to rule out TB. If you've got early HIV disease

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and you are completely well, completely well, you have no symptoms, do I believe you have TB, active TB? I don't, and I think safely there we can give preventive therapy and have a good benefit and prevent that person having to suffer the misery that is having TB, so that is why I really think we have to focus on those people with early HIV. So I think that was part of the question. I am going to hand the rest of your question onto Diane, I think.

Another question that has been sent up is also talking about what preventive therapy should be used in countries with high isoniazid-resistance rates and this is a challenge. The work that has been done on preventive therapy has largely been done using isoniazid and people have used rifampin containing regimes, rifampicin and pyrazinamide has particularly been tried. The problem with this regime, it works fine. It does have higher toxicity levels and I think there have been really no studies looking at good preventive therapy regimens, particularly by those multidrug resistances as a big issue, so currently we don't know so the question from Vietnam where they say they have isoniazid resistance of 20- to 25-percent, we don't know. There is no evidence for other regimes and so this is a big problem.

DIANE HAVLIR: So two questions I have, the first was in a second-line protease inhibitor containing regimen, how

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long do you need to continue with the boosted PI after completing TB treatment?

I think one thing for second-line regimens, we would like all patients on second-line regimens to be on a boosted protease inhibitor. Certainly if there is not access or cost is a reason, it would be better to be on an un-boosted protease inhibitor if that is the only available option. And in that setting, because of the persistent hepatic anti-inducing affects of rifampin, probably somewhere in the range of one to two weeks. But once again, I would emphasize we were switching rather late with our monitoring capabilities right now that second-line regimens using protease inhibitors are best using boosted protease inhibitors.

The second question really echoes one of our major challenges, which is the resource one and the question was countries are using INH withambutol because they can't provide or assure DOT, and I think this gets back to resources. We should strive for what is best for our patients. We should lobby to get the resources to provide that but if we can't do it, it doesn't mean that we do nothing at all but we do the next best thing.

SOUMYA SWAMINATHAN: I have, it's more of a comment, I think, which says that India now has 5.7 million people, according to UNAIDS. We are now the nation with the highest number of people living with HIV/AIDS in the world and do you

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think it helps to continue patting ourselves on the back about being a low-prevalence country?

Well, yes, we do have the highest or the second highest number of HIV-positive people in the world. It is debatable but because of our huge population. Obviously prevalence-wise, we are way below many of the African countries at 0.9-percent. Certainly there is no room for complacency, but the reason for the presentation being designed like this was that the challenges are different in a setting where 70- or 80-percent of your TB patients in a clinic are HIV-positive versus a clinic where maybe four or five or, at the most, 10-percent are going to be HIV-positive.

So that was the reason, really, for the experience from these two countries to be presented separately, because how do you go about testing, how do you identify these people who are HIV-positive and how do you link them up with HIV care, which may not be as widely available?

The other question is about in a child with TB/HIV coinfection under the age of 3 years, what is the optimal ARB combination? Since [inaudible] 3TC zidovudine is a recipe for aortic failure should we continue to use nevirapine but introduce Ambutol into the regimen? Well, as Dr. Havlir just mentioned, I think the ideal TB regime does not doubt that we should use a rifampicin containing regimen. So in a child as

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well as in an adult, we would use the six-month rifampicin-containing regimen. Since we cannot use efavirenz in a child under the age of 3 years, the options would be to either use nevirapine but then use it at the higher dosing level of 200 mg per sq. meter per dose or to use a triple NRTI regimen, with which I don't think there is much experience in children.

ELIZABETH CORBETT, PhD: [Inaudible] can I ask you to answer your questions?

MALE SPEAKER: Yes we have two questions for Diane and coming from Congo and from Kenya. They want to know more about the immune reconstitution syndrome, if it's a failure, and how do you manage this [inaudible] syndrome, for Diane?

DIANE HAVLIR: The term immune reconstitution syndrome has created some confusion because it has been used in two entirely different settings. I am inferring from this question what it means is what was first called paradoxical reactions and that is you have an individual who has tuberculosis. They are treating with TB treatment and they get transiently worse clinically. This actually happens in HIV-uninfected persons but it happens more commonly in HIV-infected persons. The main manifestation that we see in this syndrome is fevers, worsening pulmonary disease, and we can see expansion of CNS lesions.

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In the HIV-infected persons, this is a very complicated clinical issue to manage because there are about five things that the clinician needs to think and ask themselves is it going on. Is this TB failure? Is this malabsorption? Is this an adherence problem? Is this another new entirely diagnosis? And in HIV we often see patients with multiple opportunistic infections.

However, in patients who other causes of worsening have been excluded and in patients where adherence has been checked and everything has been done to exclude other possibilities, what we do is we recommend to forge ahead with the antiretroviral therapy and if steroids are needed in that case, then we give our patients steroids.

I actually had included - this is a great question - I have included as one of my challenges in that my talk was too long so I took it off, but clinicians can commiserate among themselves, often it is very difficult to get our patients off steroids once we do this and there is always a questioning what one does of him or herself when this happens and is it really immune reconstitution?

ELIZABETH CORBETT, PhD: I have one question from Dr. Medlin, I'll be presumptuous enough to answer myself, which is about the question of presumptive treatment for smear-negative and extrapulmonary TB in HIV-positive patients in settings where there is access only to smear as a diagnostic

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method and I think Lucy's experiences would have been less grueling and having good framework in which for her clinicians to take forward the diagnosis of smear-negative TB in rapid steps. And there has been a WHO working group aiming to provide such kind of guidelines and those will be published later on this year with the aim of trying to get that whole diagnosis process down to two or three weeks at most.

So certainly we will say yes, most definitely a place, we certainly - I don't think anyone would be suggesting that only smear-positive TB patients are treated and guidelines for those will be coming out. And the main problem is just a reluctance on the part of clinicians to subject people to TB treatment if it's not clear in their own mind. So we will have to see how these new guidelines which will be subjected to evaluation work out.

PAPA SALIF SOW: We have another question for the panel from the audience. They want to know what is, of course, the culture, sputum culture, in Zambia, in Kenya, in Rwanda and also in India? Is it possible, is it difficult to do the culture?

HELEN AYLES: Well, in Zambia it is difficult to do sputum culture in that until recently, we had one national reference laboratory that did sputum culture and the main teaching hospital in the capital city. We just got another

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sputum culture site in the country and we have been using solid media, egg-based, made on site.

We are trying, as part of the fine demonstration projects of liquid culture, we have just introduced the liquid culture systems which the prices have been brought down for developing countries to try to improve access to culture but it is still not cheap. It is still much more expensive than smear and much less available.

SOUMYA SWAMINATHAN: In India, also, the microbacterial culture facilities are available only in very few reference laboratories and even maybe four or five and even fewer candescence, drug susceptibility assays, or there are some private laboratories that offer liquid culture media using [inaudible] but they are very expensive and so not accessible to those populations who are actually getting TB.

ELIZABETH CORBETT, PhD: Okay, we are on to our final question now, because the session is about to finish. The question is for Helen. What is the benefit of TB prevention in HIV-positive patients in countries where there is a high chance of reinfection?

HELEN AYLES: Yes, this is one of the issues that I talked about with the duration of therapy because as I showed that slide, a six-month course will give you protection for a period of time and then that protection wears off and we think that is probably due to reinfection. So the question is

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whether we need to do post-courses of therapy or whether we need to give continuous isoniazid preventive therapy like we do with antiretroviral therapy, whether we just have to start people and continue them.

And the answer is not no, but the study is ongoing. It is going in Botswana. I am told they have recruited the cohort and they are now following them up but of course as you can imagine it is a long study because how long do you need to wait to know whether you are giving benefit? But my personal opinion is that we are going to have to give repeated courses or just keep isoniazid going for a long time.

ELIZABETH CORBETT, PhD: Okay, thank you very much, and I thank the audience for coming and each of the panelists for their contribution to this. Thank you.

[Applause]

And I hope that everyone agrees we are making tremendous progress on TB and HIV issues, and I am sure we will have much more progress in the next two years.

[END RECORDING]