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DIANE HAVLIR, M.D.: Welcome to Sydney and to the HIV/TB Satellite Symposium. My name is Diane Havlir. I am professor of Medicine at UCSF and chair of the Stop HIV/TB working group. My co-chair for this symposium is Dr. Soumya Swaminathan. Soumya is a pediatrician and she is a TB researcher and leading the HIV/TB research program at the TB Research Institute in Chennai, India.

I would like to thank the Sydney organizing committee for allowing us to have this symposium, to the IAS for featuring HIV/TB quite prominently in this meeting. I'd like to thank the symposium planning committee speakers of participants which are listed here, and the many sponsors for the meeting. I would particularly like to thank Veronica Miller for all the work of herself and her staff from The Forum on HIV collaborative research and Hili Jesus Getihom [misspelled?] from the WHO for his work in putting this symposium together.

Veronica asked me to call your attention to a special supplement on HIV co-infection which is available online and will be a print edition in August.

So as we all know, living with HIV in most parts of the world means living with TB. Although TB's a leading cause of death in persons living with HIV, we've yet to define optimal

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strategies to treat and prevent both diseases. This symposium is designed to highlight research priorities, and ask a panel of some of the most influential leaders in the world on HIV, about their vision and commitment to HIV/TB research.

As way of background, I would like to say I think we've seen an impressive scale up of resources for implementation of HIV and TB activities through the global fund. This year, for example, Petfar allocated an additional \$50 million specifically targeted as plus help funds for HIV/TB activities added to the \$70 million leading to \$120 million for implementation of HIV/TB activities. Despite this acceleration in implementation funding, I would say honestly research has been slow out of the starting gate. As you'll see in the symposium today, there are many unanswered research questions that we already know of, and certainly as of the rollout goes forward many new ones are already arising. This then is the focus of this symposium.

And this is the challenge: While we are accelerating implementation, how do we support financially and conduct research that improves outcomes of both diseases? It is our hope at this meeting in Sydney that we look back as this as a turning point of the commitment and action dedicated to HIV.

The way this symposium is going to be set up today is that we are going to have four speakers give 10-minute

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presentations on four priority areas in HIV/TB research.

Following that we will ask our panel to come up to the front and each individual on the panel will be asked to speak three to five minutes about their vision and commitment to HIV/TB research. This will followed by an interactive discussion among the panel members and with the audience about priorities and way forward in HIV/TB research.

So without further ado, I'd like to introduce our first speaker, Dr. Stephen Lawn, familiar to many of you. Stephen is a faculty member at the University of Cape Town and at the London School, very active and prolific, a researcher in the HIV/TB area, incredible on-the-ground experience, and he's going to summarize with us the research priorities in HIV/TB.

STEPHEN LAWN, B.MED.SCI., M.B., B.S., M.R.C.P., M.D., D.T.M&H., DIP.HIV.MED: Good afternoon. I'd first like to thank the organizers of this symposium for asking me to speak on this important topic, research priorities in HIV/TB. I'm going to start by setting a scene, just briefly describing the impact the HIV associated TB epidemic on TB global control. Thereafter I'm going to illustrate some of the key research priorities using data from Cape Town. So it's very much a view from the field. And then finally, I'll address a very simple question: Why should TB/HIV research be such a high priority?

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In 2005, it's estimated that 2 billion people were co-infected with mycobacterium tuberculosis. There were 8.8 million new cases of active TB and 1.6 million deaths. The vast majority, some 7.4 million of those new cases were in Sub-Saharan in Africa or Asia.

In most parts of the world, TB instance rates have been declining since 1990, in middle and industrialized countries. In two parts of the world, the former Soviet Republics and particularly sub-Saharan Africa, those countries with high HIV prevalence, TB instance has been steadily increasing. HIV has been particularly an important factor underlying the 1-percent global rise in annual TB instance between 1990 and 2003. There are signs that the tide might be turning, that TB instance rates are declining. But it's a sobering thought to realize that in the middle of the first decade of the 21st century there have never been so many new TB cases each year, in the world today as ever before. And there's a lot of work to be done to meet the Stop TB partnership goals to reduce TB by 2015.

The HIV/TB epidemic is principally concentrated in the countries of southern and east Africa, where over 50-percent new TB cases are also HIV co-infected. In Botswana, when a DART strategy was introduced in the mid-'80s, subsequent to the that, TB instance rates steadily increased from 1990 onwards due to the impact of the HIV epidemic. It's becoming

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increasingly clear that the DARTs, to be a strategy, is insufficient alone to control this epidemic. In 2005 a WHO meeting of regional ministers declared this epidemic was a regional emergency requiring urgent and extraordinary actions. That makes the question what are those urgent and extraordinary actions? I think the truth is we don't really know what we need to fuel this activity as urgent and extraordinary research.

I have the privilege of living and working in Cape Town, South Africa, for the past two to three years. I'm going to describe the challenges of HIV and TB in this setting, in the TB clinic, in the community and then the antiretroviral clinic. This township in the south peninsula is a working marketed township of around 13,000 people. It's a poor township and has a single primary healthcare facility where TB treatment occurs using the DARTS strategy. Within this clinic there's been an astounding rise in the burden of TB. Rising number of cases per year, rising from around 30 per year to nearly 180 per year. And there's been a disproportioned increase in extrapulmonary and sputum smear negative TB, which is obviously difficult to diagnose and presents a huge challenge to a limited staff in this clinic. Two-thirds of these people are HIV infected. Re-treatment rates have increased from 3-percent to 24-percent despite the use of a 6-

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month resumption-continuing regimen. Eighty-seven-percent of those re-treatment cases are HIV co-infected. Mortality rates among HIV/TB co-infected patients in sub-Saharan Africa are high, up to 30-percent of patients dying during the course of TB treatment, in the absence of antiretroviral treatment. Within the community, the rates are staggering in this township. Between 1996 and 2004, there's been an increase from around 500 cases per 100,000 to 1,500 per 100,000. And this has been periled by the increase in HIV prevalence from 6-percent to 22-percent among adults.

Using this AID-stratified analysis, the number of TB notifications on y access can be seen to increase year by year, what each of these subsequent lines – difficult without a pointer I'm afraid—but you can see that the predominant increase has been among 20- to 49-year olds. You can see that in 1996 the TB instance rates steadily increased with age and adulthood. But since then, in 2004 the rates increased staggeringly among 30- to 49-year olds these rates have reached 3,000 per hundred thousand. There's also new epidemic of TB among adolescents, traditionally the golden period of TB. And you can see that on the lower graph HIV prevalence has plateaued from around 2001. But despite that, the TB notification rate—the line above that in solid—has increased with an ongoing amplification, the TB epidemic, despite that

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plateau of HIV prevalence. It's a presumption to ongoing evolution of the level of immune deficiency among that population.

If that burden of TB isn't staggering enough, when you do active case finding, the story gets worse. A 10-percent population sample was studied in this community and the HIV prevalence was found to be 23-percent. Three-percent of the population also had TB. In black, it shows TB that was already diagnosed, but in red and yellow is the proportion of TB that was microbiologically proven but has yet undiagnosed in the community. Nine-percent of HIV infected patients had pulmonary TB, only 5-percent had been diagnosed in the clinic. The case finding proportions among HIV negative TB was reasonable at 67-percent. But among HIV infected patients it was only 37-percent. So there's been a staggering increase in TB caseload in this community, and this has been replicated right across southern Africa. There's a huge burden of undiagnosed TB among HIV infected patients. And warning symptoms were poorly predictive. DARTS alone is insufficient. And in this community, the DARTS program has been running since the mid-'90s with reasonable cure and treatment outcome rates.

So there are many issues. How to best diagnose TB in this setting? How can improve DARTS? What adjunctive strategies do we need to supplement DARTS, active case finding,

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mass of prophylaxis? What are the sources and the science of TB transmission in this community?

The challenge of TB and antiretroviral treatment clinic. TB has been concentrated in antiretroviral treatment clinics such as one in Guglethu, the township next to the airport in Cape Town. When patients refer to this clinic there's a one-month screen interval to prepare the patients for treatment and to diagnose TB and other opportunistic infections, and then they start treatment. Again, the burden of TB is staggering. Fifty-two-percent of patients enrolling have had one or more episodes of TB previously treated. A quarter of active prevalent TB, either recently started on treatment, or as yet undiagnosed. And a further 10-percent developed TB during the first year of treatment. And overall a third of our patients have overlapping TB treatment and antiretroviral treatment in the first year. The burden of TB during treatment decreases sharply. We can see in the first three months the rate is extremely high at 23 cases per hundred person years. All the patients had new onset on symptoms in the three months of ART. And undoubtedly these patients had sub-clinical TB at the time of screen that wasn't detected. This raising an important question, how do we exclude or how can we diagnose this TB before we start antiretroviral therapy? Secondly, you'll note that the rates at the end of the first

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year is still 4.5 cases per 100 person years. And the rate plateaus at this in the long-term, after three years, it's still 4.5 cases per 100 person years. So rates don't reduce the background during antiretroviral therapy. And on the right there you see that the rates 4,500 per 100,000 is many fold higher than the background rate in the community among HIV negative or in the whole community. And so with these patients living much longer during antiretroviral therapy the contribution of TB to the community is much greater from these survivors. And this will potentially undermine any beneficial effect of ART on TB control.

So there are many questions arising from this had we screened for TB on arrival of the antiretroviral treatment program. There are many issues relating to the delivery of concurrent treatments. How do we diagnose, manage and prevent TB immunosuppression disease? Infection control is a huge issue, and the effects of antiretroviral therapy on TB control.

There's a very broad research agenda but it can be broken down into four main categories. We need basic epidemiological research to measure the burden of TB in these communities and measure the impact of interventions. We need research on new tools and interventions, new diagnostics, screening tools to detect TB more easily. We need new treatment strategies. We need research to improve existing

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interventions such as DART, such as isonizide prevention therapy. And we need health policy systems research to see how all this can be delivered within the confines of health systems in these developing countries.

So I'm just going to highlight five of these key research areas. Diagnostics, case finding, preventive therapy, infection control and integration of TB and HIV services.

We're using a diagnostic test in most parts of the world that was invented 120 years ago. And among patients with HIV and co-infection the sensitivity can be as low as 20-percent, which is wholly inadequate. There are many new TB diagnostics on the way. Serology is very easy to use but has very poor performance. More highly performing technologies though are not easy to use and are not applicable at the point of care. We are desperately in need of a test that can be applied within the clinic. In our clinics in the township, we can diagnose HIV within 50 minutes using a rapid test. But with TB diagnosis, often we're waiting three weeks for result of a sputum smear or a sputum culture. And we are fortunate to have culture facilities available in Cape Town.

Active case finding, there are many unanswered questions. How can we target HIV infected patients more easily? How can we increase VCT efficiency? What other groups should we be targeting through disease transmission?

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We need an effective screening tool, a new diagnostics. Isoniazide as a preventive therapy. It seems that many working in the field regard this as a very effective intervention right under our noses, but there are many questions remaining. Although it clearly works how can we implement it? How do we exclude active TB before starting treatment, that we don't give isoniazide immunotherapy to active TB unwittingly? What is the risk of drug resistance? How long should we treat? How can we improve uptake in compliance? How can we overcome issues of co-toxicity with other drugs? There are confusing data rising from Botswana, from the CDC BOTUSA project. In 2003, initial studies seem to show that to exclude active TB, symptoms and signs when adequate screen, a chest X-ray was not needed. But at CROI in Los Angeles in 2007, it was found that 12-percent of asymptomatic HIV infected patients had an abnormal chest X-ray, 9-percent had active TB. And it did, in Cape Town, and elsewhere in Tsenzisarua Zimbabwe, studies are finding high rates of sub-clinical but active TB. And these could obviously be a source of isoniazide resistance, if we roll out IPT programs. A meta-analysis showed that there was a trend towards an increase in resistance, but this was not significant. But the risk was made much higher in high TB incidence settings, under normally search conditions. It seems that no data exists to show that isoniazide through prophylaxis does not increase

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resistance, but we cannot be sure on this. The country policies on IPT reflect this confusion. Bezwada has a program for HIV infected individuals, but now the screening strategies are somewhat confused. Kenya has dismissed IPTs and intervention after national consultation. And Burundi has funding for an IPT program but now wants to reprogram this into operation research to answer the many unanswered questions.

Infection control. TB has been concentrating our ART clinics and medical wards. In Guglethu and the township I showed earlier, one in three patients has TB at program entry or during the first year of antiretroviral treatment. This is a huge hazard. How can we screen again for potentially infected patients? How can we care and prevent TB among the healthcare workers? What interventions are needed? How can we airflow in an achievable way and ultraviolet light? What is the efficacy of these interventions, and how can we study these?

Then integration of TB and HIV services is important but some areas need a lot of work to make them happen. And this is no exception. In Guglethu, our TB and antiviral clinics are a mile apart and run by separate city and provincial administrations. We need good models of how integration can be achieved at national, regional, district and clinic levels. We need to demonstrate the benefits. It's hard

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work making these systems come together and people have to really buy into the benefits of this. We need to overcome concerns about nosocomial TB transmission and of the difficulties.

And finally, why should HIV/TB research be such a high priority? I think the traditional model of research funding has been based on the following: the level of interest from pharmaceutical industry interest groups, the level of advocacy, media exposure and donor interest. Secondly, how answerable are the questions? And thirdly, how attractive are the data to the research community? Are they novel and are they publishable in high-impact journals? I think a novel approach is needed. What is the potential of reduction in disease burden? What is the impact inequity? Is it answerable? What is the likelihood of efficacious interventions being developed, and will it be deliverable?

I'll put it to you that in the case of TB and HIV/TB, all these are yes. The burden of TB is huge and its impacting communities that are the most underserved and underprivileged communities on earth. These questions are answerable. We will, and can find interventions if we put our minds to it, and these are deliverable on a large scale. So let's go back to Maputo in 2005. A regional emergency requiring urgent and extraordinary actions. These urgent and extraordinary actions

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must be informed and made possible through urgent and extraordinary research.

I'd like to thank my colleagues at the Desmond Tutu HIV Center in Cape Town, Robin Wood and Dr. Keren Middelkoop, Glenda Meyer and Machusin Bandree [misspelled?] and the rest of the staff there. I'd like to thank Halley Yaesosketchivon [misspelled?] from STOP TV and WHO for his discussions regarding this talk. I'd also like to thank the Workam [misspelled?] Trust who fund me and the NIH who funded some of the studies in the townships and Cape Town. Thank you.

DIANE HAVLIR, M.D.: Steve, thank you very much. That was a terrific distillation, I think, of the key issues and where we're at, particularly with the operational research questions. When we have the discussion period, if you have questions for Steve, he'd be happy to answer those during that time period. What we'll do is just go consecutively through our four speakers.

So our next speaker is Dr. Jerry Friedland. Jerry is professor of medicine at Yale University. Jerry, along with his South African colleagues, recently reported the outbreak of XDR in Tugelaferi [misspelled?] and [inaudible] in the Lanset and we asked him to come and speak about XDR and the research priorities in this area. Jerry.

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GERALD FRIEDLAND, MD: Good afternoon, colleagues and friends. I'd like to thank the organizers as well and all of you for gathering for this session. I'm going to follow up on many of the issues that Steve discussed, but more specifically related to XDR and MDR-TB, as is my challenge.

In some ways, this has been the year of MDR and XDR-TB, starting out a little more than a year ago with the CDC WH report on the global XDR-TB [inaudible], the first time that XDR-TB had been defined. It seems like we've been living with that term for a very long period of time, but it's only a little more than a year. The global distribution, the fact interestingly and importantly that Africa, India and Southeast Asia were notably largely missing from the representation of XDR cases, not because they don't exist but because they hadn't been either the technology was not available to identify them when it hadn't been reported. And also, HIV was not recorded in that report because this was entirely from TB Super National Reference Laboratories. Soon after that our own report in rural South Africa and Tugelaferi appeared and with much higher than expected rates of both MDR and XDR-TB, clearly HIV associated in that 90-percent, actually 100-percent of those identified with the XDR-TB were also HIV infected. There was clear evidence of nosocomial transmission and an extremely high mortality of 98-percent in the 53 cases that we identified.

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Since then, there have been global burden estimates of MDR and XDR-TB with 400,000 to 26,000 respectively, of each these of course are estimates. Many expert meetings, recommendations, WHOs, CDC, NIH, The Forum, national and international meetings such as these. And then very recently there was the ASPI, which I'm describing as the airborne single patient event, which also contributes enormously to this issue. So when the first report came out in March 2006 there were 17 countries on all the continents that were known to have XDR-TB confirmed cases. And since then to May, one year, there are now 37 countries that have reported XDR-TB, and those are listed and also seen on these red dots. And again, if you notice, Africa, India, most of Southeast Asia, the place where the world's greatest burden of TB is not really represented in these figures. And in addition, these data are really anecdotal, referral samples and not really population-based, so that we really don't know the incidence or prevalence of XDR or MDR-TB in most of these areas, and certainly not XDR-TB except for just a few countries, Korea, Lafiad, the United States, also little Tugelaferi in South Africa.

So MDR and XDR-TB, I think we could say, uncovers past and current deficiencies in TB knowledge, strategies and programs, and clearly illustrates the global nature of TB drug resistance. And for high TB and HIV prevalence areas, it

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threatens the success of both stop TB and historic antiretroviral rollout, in addition to the disastrous consequence to individuals and communities. And for high TB and low HIV prevalence areas with HIV incidence of any parts of the world, it really alerts us to an ominous danger into the future.

So I'm going to focus really more on elaborating research priorities in this area, although I will address and present some bits and pieces of data that I think would be interesting to you. So there are really broad and complex areas of need of course in epidemiology, in diagnosis and treatment, in organizational issues and delivery of services. I think we tend to get overwhelmed by this entire enormous array of need and it's useful to try to define them in short- and long-term approaches, goals and solutions. So we can focus efforts I think initially on really what short-term goals, what short-term issues, what short-term approaches would be really have the greatest impact in what is, in many parts of the world now, particularly in sub-Saharan Africa, an emergency situation. Among these things, I think, and it was mentioned, operational research strategies are essential and of course implied in all of this is an enormous increase and need for resources. And I won't discuss that - there will be plenty of people on the panel who will.

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So I wanted to get back to these two, what I'll call case studies of MDR XDR-TB of the Tugelaferi situation, and also the ASPI, or the airborne single-person event. And on the face of it they would look like they're extraordinarily different events in the course of tuberculosis, and drug resistant tuberculosis. In Tugelaferi, there's high TB, MDR, XDR and HIV prevalence. The 53 cases that were originally reported, now actually for MDR are over 450, and 55-percent of them, or 260-some-odd cases, are XDR-TB and 45-percent MDR. So on in a period of about two years the figures have actually increased five-fold. On the mortality, if there's any good news, has dropped from 98-percent to 85-percent, but unrecognized, and I think without enough attention the mortality among individuals with MDR-TB in this environment approaches 65- to 70-percent, and 90-percent of individuals are HIV co-infected.

So that's one part of MDR/XDR, and now we have the single case, by way of contrast. But there are a lot of similarities between the two that actually, I think in many ways illustrate the deficiencies, and places where we need to go in terms of our priorities, as different as they are. So there are diagnostic limitations in Tugelaferi in South Africa with no microbiologic monitoring as TB therapy has been used over the last decades. So no real appreciation of the increase

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in drug resistance and new diagnostic limitations, and delayed and discordant, and very confusing results, with ASPI both reflective, I think of the deficiencies and neglect in tuberculosis diagnosis over the years. Standardized treatment for both in the face of this in Tugelaferi and in Sub-Saharan Africa is partially responsible for amplification of drug resistance. And standardized therapy in this instance with the individual case was initially, of course, inadequate inappropriate, but without documentation of what drug susceptibility might be. In Sub-Saharan Africa TB control programs very poor outcomes. The HIV epidemic and this KwaZulu strain, which appears to be at least as virulent, certainly no less virulent than other strains of tuberculosis, have all contributed to this firestorm. We don't have too much to say about the individual case, but clearly lack of attention to transmission, and what I would say puzzling and almost unbelievable attention or misattention to transmission. And the individual case really highlights the issue of transmission of MDR and XDR-TB. In this instance, in very different settings in community and in an airplane at 35,000 feet.

The absence of treatment options, or the limited treatment options that both situations really illustrate, and a whole array of ethical dilemmas, which time won't allow to go into, but are raised by this issue of individual health versus

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public health. So they're not so far apart actually and there's a lot that we can learn from both of them. So I'm going to go through some of those areas that I mentioned very briefly.

So in terms of epidemiology, there's a desperate need for epidemiologic characterization interventions, and I'll classify them roughly and somewhat arbitrarily, but I think usefully at the short-term and long-term interventions and characterization. We really need to have a more rapid response to investigate hot spots of XDR and MDR-TB, and not rely upon the standard WHO surveillance procedures. This is really an epidemic situation and not one of continuing tracking of epidemic resistance trends of over time. And the response to, actually the instinct response to trying to find out what is going on has really been a rather slow and inappropriate surveillance rather than outbreak investigation response. So we really need to know more quickly what, actually, where the most important areas are. They seem to need some more work on the determination of type and site of transmission, acquired versus primary, and we feel that primary transmission has been most, most important, as well as nosocomial and community with nosocomial predominantly, and interruption of transmission. With all of the diagnostic, therapeutic, questions that might be asked and resolved in the short and long-term, probably the

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most important thing that could be done quickly is to think of strategies that would result in interruption of transmission now. And many of those revolve around infection control procedures; practices that are implementible even in resource-limited settings, but have really escaped notice or attention and desperately, desperately need to be addressed. In the long-term, of course standardized surveillance is critical and understanding relationship between resistance virulent-specific strains. Biologic approach to understanding epidemiology and transmission is critical.

Turn to diagnosis in the short term and long term, there's a desperate need for modern, rapid MTB diagnosis, drug susceptibility testing, first and second-line at the point of care was pointed out. In terms of short-term, I think we still need to explore the idea of trying to separate out by clinical algorithms, and maybe mycroscrocity [ph], those individuals who are more likely, rather than less likely, to have drug resistant tuberculosis. And identify and apply some sort of separation strategies and not enough work has been done on that, and that could be done quickly.

Expansion and availability of existing technologies, there are opportunities to expand. The laboratory procedures that we have, although inadequate in terms of time, but nevertheless essential in terms of making the diagnosis of MDR

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and XDR-TB. An expansion of second line drugs susceptibility testing in existing labs that do culture – most of the labs in Africa and in South Africa that are able to do TB culturing and drug susceptibility testing have not been doing second line drug resistance testing. And if we're having to the diagnosis of XDR-TB, you can't.

Testing available, promising rapid tests, mostly rifampin-based as you know, when expansion of rapid testing includes sentinel second-line drug susceptibility testing the rapid tests that we have now are all rifampin-based. And that will not get to the issue of XDR-TB, but only MDR-TB. In the longer term, once these rapid tests are shown to be useful, widespread availability, then I think we need enhanced and more respected approach to diagnostic research, which sort of is somewhere in the operational, translational or applied, and doesn't have the same credibility as more basic research. But in this situation I think we're really witnessing some of the problems that that has caused. So encouragement for diagnostic research is incredibly important. And one of the greatest effaces in this whole area is the training and retention of laboratory personnel in resource limited settings.

And I'll just very quickly mention the desperate need for new drugs and shorter regimens, but in the short-term I think there are opportunities, as with HIV, to speed up drug

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evaluation and approval with tuberculosis, and I've listed some of those. It's important to know about drug interaction with second line drugs and HIV, and it's incredibly important to develop novel treatment, delivery, strategies for second line drug treatment. In KwaZulu, it's still required that you go to the central to the hospital in Durbin in order to start second line therapy. And there's a six-week wait in order to actually been seen, and this is true in other parts of South Africa. So that how we can possibly actually address treatment even if it's available under those circumstances? It needs be decentralized and community-based, and I mentioned a number of long-term treatment issues.

In the issue of HIV and TB, it was mentioned universal access to antiretroviral therapies. Critical to decrease susceptible population. It's probably the best treatment we have now for XDR-TB is actually improving in the incompetence. Strengthening TB programs, of course, in operational research or programmatic aberration and integration.

And again, to say one more time, there's an urgent need to interrupt transmission. And just to give you an example, on the left is an individual who was treated for drug susceptible tuberculosis successfully and three months later new area, new lesion, had acquired XDR-TB nosocomially and expired.

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In the short term, the focus on developing, implementing and monitoring site appropriate infection control strategies and study the effectiveness of these strategies individually and in combination.

I'd love to show you these, but perhaps at another time, but just conclude that in the long term, of course, and this is very long-term we need vaccines and alleviation of the social and economic conditions and health disparities that breed both TB and HIV. Thank you.

[Applause]

DIANE HAVLIR, M.D.: Thank you, Gerry. I know there's a lot we can discuss on MDR and XDR, but we are running out of time so I would like to invite Dr. Mark Cotton. He works at the Stellenbush University [misspelled?], the Tygerber Children's Hospital in South Africa, and he is going to speak to us on pediatric populations. "What is the Research Agenda?"

MARK COTTON, M.D., Ph.D.: Good afternoon, everyone, and thank you to the organizers for asking me to come and speak to you. These are some of the areas that TB and HIV have in common, and there are quite a few of them. I'm not going to read through all of them, but they include biomedical and social adherence issues as well to just comment on point number six is that virtually every child who has neglected HIV has

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chronic lung disease and when one needs to diagnose TB on the background of chronic lung disease.

So, how many clinical trials have actually been done in childhood TB? And this is a [inaudible] that I attended just in preparation for this talk, and I had to look quite hard and this is what I found. There are not many actually when you consider how many children are treated for TB. So, childhood TB does contribute significantly to the case load and the estimation is about 14-percent of the total burden and incidence in children in the Western Cape is around about 400 per 100,000.

So, TB is very common in HIV infected children and incidence data was worked by Heather Zore [misspelled?] and myself and colleagues and in the Western Cape in the limited access to anti-retroviral and therapy and it's 23.4 of each 100 HIV affected children will develop TB each year.

TB is also common in pneumonia, and this is just the most recent evidence that comes from Dessa McNaly [misspelled?] and colleagues from [inaudible] and what you see is in patients both HIV infected and uninfected presenting with acute pneumonia and not responding or getting better within 48 hours, you can look at the large percentage of children especially HIV infected who have acute pneumonia that is due to TB. So, the presentation and outcome diagnosis have been fairly well

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described in some perspective and a lot of retrospective studies. The biological and immunological outcome in children are well described and there's not that much long-term data on HAART. This is in the absence of HAART to showing how TB exacerbates the HIV-related mortality through a study from Ethiopia.

One such study that's helped with the clinical description is from Anica Hislan [misspelled?] where she documented a poor response to standard and MTTB therapy and a high mortality often due to opportunistic infections and also recurrent tuberculosis in culture confirmed cases. So, the diagnosis of childhood TB is certainly in the absence of HIV is becoming a lot easier and again a study by Ben Marie [misspelled?] from Stellenbush [misspelled?], who looked at symptom complex with a very, very high predictive value for diagnosing and TB. [inaudible] become more popular and with a higher yield in gastric washings and this is the data from Heather Zore [misspelled?] from Capteon [misspelled?] and then new diagnostic case are being evaluated and need to be evaluated. This slide also just makes the point of the long delay for actually translating the diagnosis of TB and especially culture confirmation and sensitivity confirmation and the long gap in time we were asked to make clinical decisions in the absence of laboratory data. Duration of

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therapy, unsatisfactory response to six-month regimen has been documented in adults and children.

A study has been completed in Capton [misspelled?] the results are not out yet, and the [inaudible] this is comparing six versus nine months and the Capton [misspelled] studies that have shown that six months is not great. So, drug resistance in children is increasing as stated from Simon Starr [misspelled?] from the Western Cape [misspelled?] and children reflect ongoing transmission in the communities and need to be considered in any consideration of drug resistance. So it is possible to do large perspective trials in HIV infected children when it's reasonable case definitions. One is radiology, skin tests, and one can get specimens for culture.

One of the important mechanisms is an end point review committee or impartial expert or experts to review cases and x-rays. This is one such study that was conducted recently, which supported INH prophylaxis for HIV infected children as a routine strategy, and there was a significant difference in death rate and none of the kids were suspected of having TB, and of course, the INH did result in a lower incidence of TB.

This is another study which is ongoing. This is the IMPACT 1041 study. The acronym is at the bottom and it's sponsored through the Division of AIDS, which is a very large, well-designed study looking at the IHN prophylaxis as a prime

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strategy in exposed and infected, HIV exposed and infected infants. Three centers in South Africa and another three in sub-Saharan Africa to open quite soon.

What about the absorption of MTTB [inaudible] in children? Not that much to my knowledge is known about this, but here's a study by Steve Graham looking at the [inaudible] in children. Of course, the absorption worsened in the young infant, young kids and if they are HIV infected. The timing of HAART and MTTB therapy has not been studied. I'm not sure if it should be. I think we should all be treated myself, and I think I'm just going to go on to the next one. In terms of [inaudible] retrovirals, the [inaudible] interaction with the fibrins [misspelled?] has recently been studied by colleagues from Capton [misspelled?] showing low levels with and without [inaudible] and also showing that lapinovir with administered retinovir gives you therapeutic levels and because retinovir is a hard drug to take with a short half-life we are now looking at double dose lapinovir/retinovir in the setting of [inaudible]. [inaudible] also increases the clearance of [inaudible] and maybe even ebacivir and I guess that needs to be looked at.

So here's a pediatric specific issue and that's VCG given to all [inaudible] in Africa, and the WHO has just given that cautionary advisory note warning about the dangers of

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immunizing HIV infected infants and even suggesting that maybe one shouldn't. VCG prevents disseminated TB and according to work by Anica Hislan [misspelled?] a retrospective study are now being confirmed in a prospective study an extremely high rates of disseminated VCG in HIV infected infants. This is some of the retrospective data really just showing, you know, that it's a problem.

The next point is that new drugs for TB, as they are being developed children, have to be included. I don't think when you look at slide number two having so few examples of studies in childhood TB and then when it comes to MBR, children have to be included as well. Beau Berman [misspelled?] from Denver has shared the strategy of optimized [inaudible] therapy plus new [inaudible] placebo and children should certainly take part in this kind of study both for treatment and for first exposure prophylaxis.

So, to summarize the research agenda, I think there's still a need for perspective and natural history studies looking at all [inaudible] of TB and HIV. Pharmacokinetics is good information. I think we need some more. VCG is an absolutely critical question that needs to be looked at very, very urgently. The new diagnostic tests need to be applied to childhood TB and transmission in health care facilities applies

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to infants as well and probably through the parents and maybe even through the infants.

I've already mentioned some of the TB issues and believe children should be involved in this. So, this is a new article on funding for TB related research, and when you compare it with the [inaudible] system and the amount of research that Small Pox gets, the amount of funding and maybe even need a bit more. I want to acknowledge some of the colleagues who helped me shape this talk and thank you very much.

[Applause]

DIANE HAVLIR, M.D.: Thank you, Mark. We know the challenge for children begins right from the diagnosis of HIV, which itself is problematic in most developing countries where access to nucleic acid test is not available, and I would like to add one more issue and that is the issue of malnutrition, which I think is cutting across all these research areas that are being mentioned. Adults and children who are malnourished definitely don't do as well both with MTTB and [inaudible] drugs.

The next speaker is Dr. Xavier Blanc. He's a pulmonologist who works at the Bisset [misspelled?] Hospital in Paris, and he's now representing the ANRS, and he's going to

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update us on "Planned and Ongoing Clinical Trials: Where's the momentum?"

XAVIER BLANC: Well, colleagues, first of all I would like to thank the organizers for inviting me especially [inaudible] to address this issue of current and planned clinical trials about HIV-TB Co-infection. So, as you consider that you have diagnosed TB and HIV, you know that clinicians face a lot of problems with the treatment because of [inaudible] burden, toxicities, immuno constitution and [inaudible], and so on, so they definitely need some strategy trials to have them. I identified three strategy questions in adult patients. Not dealing with prevention. The first one could be, which HAART regime in that situation? Second one, when to start [inaudible] treatments? And third one, how to better diagnose or [inaudible]? This later point will be addressed further at the symposium.

On the [inaudible] I used to gather this information. I only focused on recent trials that exist in international database. I'll mentioned two websites that I've accessed three days ago to check all the information and [inaudible] some of the PI's on these studies. For example, if you do query on [inaudible], mentioning TB and HIV as a condition, you will find 30 studies. The [inaudible] once you've excluded trials for prevention or [inaudible] TB, [inaudible], basic science,

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nutrition, adjunctive therapy, which is a very interesting study about corticosteroids adjunctive treatment in normal TB [inaudible] meningitis [inaudible] study and once you have [inaudible].

Second with, which HAART regimen? These are three possibilities. The one in red is the main one used in low-income settings. The [inaudible] randomized clinical trial published. So, we can face four questions in this situation. First one is the efficacy of the one study [inaudible]. Second one is it better to choose [inaudible]. Third one if we use [inaudible], 400 versus 600 milligrams per day? And the fourth one is updated on pharmacokinetics. So, I will address only ongoing trials. Not summarizing trials that hasn't been already published.

So, first question, efficacy of the HAART regimen. We have the [inaudible] study, which is a phase III French trial in co-infected patients dealing with the efficacy of [inaudible] regimen in patients. The primary end point is viral load undetectable, and it should be cured at the end of the trial. First [inaudible] are cured in January 2006. They are currently, nearly half of the target and the study will probably be completed at the end of 2008. In that study and many others, you've got a lot of similar end points. I won't get into that because of lack of time. And for each trial I

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mentioned the information for contact person so I've got email address if you want further information.

Second question, [inaudible] 400 too 600 milligrams per day so this study is becoming conducted in Thailand in 31 infected patients with CD4 cell count below 200 and [inaudible]. Primary outcome is [inaudible]. The study is starting in October. The target is 100 patients and the date of completion, the estimated date of completion should be October 2008. Again, you have got the information contact.

Now, we have got three studies dealing with [inaudible]. First one is a [inaudible] study including patients with CD4 cell count below 250 and [inaudible] TB is not mandatory. The HART regimen being tested is D4 [inaudible] plus [inaudible]. Primary outcome is also virological one. The study just started in January 2007. I've got no information about the target and date of completion.

Second study is an [inaudible] study. Roughly the same inclusion criteria. HAART regimen is a bit different. [inaudible] plus [inaudible]. HAART began the phase of [inaudible] treatments. Primary outcome is also virological one and the study started in June and is estimated to be completed at the end of December 2009, 180 patients should be enrolled. All of these studies or most of these studies only include [inaudible] patients.

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The third one is a French one, which will start in Mozambique. The design of the trial CD4 cell count below 250. [inaudible] four weeks of [inaudible] and then [inaudible]. The primary outcome is a bit different. It's also virological outcome [inaudible] at 12 months. The study is expected to start in September 2007 and target is 570 patients and the study should be completed in two years.

I want, I will only briefly mention the PK studies. I could gather three of them [inaudible] with inclusion CD4 cell count between 50 and 350 and smear positive TB. So this study is expected to start soon. Second one is dealing with [inaudible]. The third one is about [inaudible] by [inaudible] in Thailand.

Second question, when to start HAART? So, you should distinguish the level of immunosuppression. The first [inaudible] deals only with patients with CD4 cell count below, higher than 350 at inclusion and there are two arms in that study. The first one is to begin HART at inclusion. The second one is to delay HAART until CD4 cell count drop below 250. Of course, all these patients are treated for TB.

The HAART regimen is at T3C saquinavir, the study started in 2004, the target is 350 patients, the actual enrollment is 150. I'd like to mention that all the studies dealing with the timing of, the best timing of introducing IVs.

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You could imagine how difficult it is to collect such studies especially in pro-income countries, so don't be afraid of, maybe slower than unsuspected recruitment. All these studies are ongoing and recruiting quite well and quite rapidly, so, I'm quite concerned that we will have to [inaudible] for all these studies, despite maybe slow rather than speedy recruitment.

The second one deals with patients with CD4 cell count between 220 and 500 at inclusion in four African countries. It's a WHO-sponsored trial that just started. The start of the study was a bit delayed because of problems with shipping drugs in the country side, but now it's okay. All sites will begin enrollment in August. There are two arms in that study, combined HARRT with ATV [misspelled?] drugs, verses the HAART after the end of six-month TB treatment. The HARRT regimen is a T3DC process, it's a very big study with 1,900 patients and the date of completion should be 2011, not before.

The third study deals with much more immunosuppressed patients because CD4 cell count should be below 200 at inclusion. This study takes place in Cambodia. It's a good example of fruitful collaboration between two sponsors, the French NRS and NH Division of AIDS through a [inaudible]. Basically, all the patients received the same TB treatment and the same HAART regimen which is the 4TCD3 [inaudible]

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Efavirenz, the only difference between patients is the timing of introduction of IRVs, early, that means two weeks after the onset of TB treatment verses eight weeks of TB onset of treatment. The primary end point is survival. Any patients that have been positive on any smear can be included with CD4 cell count below 250, the study started in January, 2006, the target is 660 patients, the actual enrollment, 289. You can see the curve of the inclusions, which started quite slowing, but now it's increased. We hope to finish this study at the end of 2009. There are three PIs of that study: a Cambodian in one was Dr. Sactem [misspelled?], an American one with Dr. Ungleman [misspelled?] from [inaudible] and myself.

The first study is an acidity study, dealing exactly with the same question with roughly the same inclusion criteria except that as positive TB is not mandatory. Patients also have CD4 cell count below 200 inclusions. HAART is initiated within two weeks after TB treatment onset versus eight to 12 weeks after that. The primary outcome is the proportion of patients who have survived without AIDS progression at the end of the study. The study started in September, 2006 and I've got no information on the date of completion. The HAART regimen being used is Travala/efavirenz [misspelled?].

The last study dealing with this issue is what I call TB-meningitis study. Deals with the same question but in

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patients who have TB meningitis. The primary outcome is also mortality. HAART is begun immediately with TB treatment or deferred two months after the institution of that treatment.

To conclude, despite some general difficulties in funding and sometimes slower than expected recruitment, we hope that the following studies could answer these two questions in the next two or three years. First one, which HAART regimens and when to start HAART in patients treated for TB. If we have a look at a publication in January, 2006, there are still some gaps, some priority areas for research and a variation of being identified so far. This is a list of questions that still remain to be answered.

And for further information, you are welcome to read this article that will be published in the supplement issue, August supplement issue of *GID* and a regularly updated table of that paper can also be found at the following Web sites.

Thanks a lot.

[Applause]

DIANE HAVLIR, M.D.: Thank you, Xavier. I would now like to invite our panelists up onto the dais so that we can start our final discussion. Dr. Michel Kavatchkine, Dr. Deburoc Zobie [misspelled?], Dr. Charles Mangonie [misspelled?], Dr. Xavier Blanc, Dr. Michelle Zewaba [misspelled?], Dr. Kevin Decok [misspelled?], Dr. Rene Ritzon

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[misspelled?] and Dr. Barbara Long [misspelled?]. Please, would you like to join us on the dais?

What we would like to do, over the next 30 to 40 minutes is to have each of our panelists speak for a couple of minutes on their vision and mission from their agency or organization viewpoint. We've heard all the research strategies that have been listed. There are many, many challenges and many of them are clinical challenges and there are many operational ones as well and as researchers, we need to balance these two. Quite often we have answers to things but we are not able to implement them when it comes to the grounds, so I think a lot more attention needs to be paid to implementation and operization as well.

So, I'd like to invite our first panelist, Dr. Michel Kazatchkine, who's presently the executive director of the Global Fund of AIDS/TB and Malaria.

MICHEL KAVATCHKINE, M.D.: Do we speak from here? Yes? Thank you very much, Levinia and Diane. Good afternoon. I will make a few short points regarding funding by Global Fund of TB in the developing world and how does the Global Fund, in its current ways of intervening deals with some of the questions that have been discussed earlier today.

The first point is that the Global Fund is currently the major funder of TB in the developing world, in addition, of

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course, to the own effort of the countries themselves. The Global Fund currently represents the 66-percent of the overall international funding for TB. Where funding programs in 102 countries out of 130 eligible countries for Global Funding and this represents a committed about of \$1.9 billion U.S. dollars for five years. China, I must say, represents a very significant part of that funding. The \$1.9 billion, over five years, committed, also translate into almost \$1 billion for the first two years of approved programs and of that, \$1 billion or almost \$1 billion approved for the first two years, China, which represent over 20-percent major grounds there. The region, in fact, the Asian region, is largely funded in addition to China, where funding large programs in Indian and Indonesia.

The second point I'd like to make is that the Global Fund is not funding research, as you know. Not funding basic research, not funding clinical research, but the Global Fund is open to funding operational research provided that the operational research program comes to us within the country request for funding and this is an under used mechanism at this time.

The third point deals with the latter, which is that, to emphasize, but I'm sure that everyone here is familiar with that, that the Global Fund is not a up/down funding mechanism,

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where we would decide, somehow, in Geneva, you know, which would be the countries to fund with the programs which would be the programs to implement and how to implement them. The Global Fund is a bottom-up mechanism. It is up to the countries to decide on which type of program they want to implement, they would then submit a request to the Global Fund, in a round system, we know have one round per year at a fixed date, the [inaudible] offer is being launched on the 1st of March and then those proposals would be assessed by an international and independent panel of experts, and if approved, then proposed for funding by the board.

The fourth point is that because of that bottom-up characteristic of the fund, I really turn to my colleagues, particularly those who, from the UN agencies, WHO, [inaudible], to stress how important it is, to all of us, and particularly for countries that want to access Global Fund funding, that the technical agency is providing the necessary support to the countries so that TB and TB/HIV co-infection comes high on the agenda of the country and therefore, comes high in the proposals that we receive at the Global Fund. Not only would I turn to the UN agencies, I would also turn to you, Renee, and certainly to you Debra Work [misspelled?], because I know how much both the World Bank and Gates, to some extent, fund the [inaudible] society and it is, as you know, the entity that

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writes a countries proposal that comes to the Global Fund. It's not the governmentally entity, it is what we call a CCM that brings together the government, but also the civil society and we know that the nongovernmental sector is particularly important in implementing TB care in a number of countries, particularly in the Asian region. Then it's as important, I suppose, that the civil society, the nongovernmental sector is empowered and funded to be a strong implementer and strong participate in the design of the ground that are submitted to the global fund. In fact, our board has recently encouraged now, the countries to submit to us, proposals where what we call, dual-tract funding which is when, where one principal recipient would be from the government, the other principal recipient would be from the civil society or the non-governmental sector. This is already the case for some of the major TB growths for example, in India.

My last point will be that the Global Fund mechanisms for funding are not adapted to respond to an emergency, because of our round system, because of the time to respond to the call for our offers and then the time to assess the proposal, to sign the ground and to start bringing in the funds. We do have to look for complementarity with other mechanisms that could respond to emergency situations. And Jerry, you clearly pointed out the necessary of having mechanisms respond to emergency and

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I'd just like to inform everyone on here that we're in current discussions with Unitate [misspelled?], a road map will be designed together with Unitate and proposed to the board of Unitate and the board of the Global Fund in September and October and in the mechanism we are trying to work out with Unitate, Unitate will be in a position to immediately respond to an emergency and send in drugs for resistant TB or funding for XDR-TB at the condition that at the same time when the country receives or agrees to receive funding from Unitate or drugs from Unitate, the country would commit to submit an application to the next round of the Global Fund, so that will then have the Global Fund coming as a relay to Unitate.

These are the points I wanted to make and I'll stop here. Thank you.

DIANE HAVLIR, M.D.: Thank you. I'd like to ask Dr. Dr. Deburoc Zobie from the World Bank to speak.

DR. DEBUROC ZOBIE: Thank you, and thank you to the organizer just for inviting the Bank. What I would like to do in the three minutes that I have is to, first of all, tell you where the bank is involved and then raise some of the issues.

Up front, what I would like to say is compared to the response the bank has shown to HIV/AIDS, we are self-acknowledged that we haven't paid that much attention to TB and this is something which we have picked up recently and

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hopefully would be implementing this much faster and much closer to our involvement in HIV/AIDS. The enrollment of the bank, both on HIV/AIDS and TB, is in many countries in Africa, Asia, Latin America and the Caribbean, most of the examples I will be using will be from Africa.

We support TB programs in a number of areas. The first one is through the sector-wide approach, where a substantial amount of resources, more than about \$7 million dollars, go into the strengthening of the health sector in terms of budget support and systemically strengthening service delivery, which includes HIV/AIDS.

The second area is the multi-country HIV/AIDS program for Africa, a billion-dollar project and \$155 million-dollar project for the Caribbean in these, again, a substantial amount of this fund has been going into TB treatment. More importantly, the treatment acceleration program that we have in three countries in Africa was [inaudible] to roll out HIV/AIDS treatment, has TB services as part and parcel of this treatment.

We have, as many of you know, we have just concluded a health system strategy for our health nutrition and population unit of the World Bank and part of that strengthening of national health systems would be strengthening delivery of TB and related infections.

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We also put a lot of emphasis in increasing our analytical work and policy dialogue with countries regarding TB. More importantly, we are harmonizing and working very closely with efforts of the World Health Organization, the Global Fund, the Stop TB initiative and, more recently, the Africa TB Hybrid Coalition, where the bank would be playing a significant role.

We would also use our analytical capacity to conduct assessments in selective hybrid countries to determine financing and program [inaudible], as well as opportunities for stronger collaborations between HIV/AIDS and TB programs that the bank indirectly has funding.

XDR-TB, like other organizations, we have also focused on it and the bank is working very closely with the XDR Global Task Force.

More particularly in the Africa region, we have now revamped our personnel to deal with TB and there is a new strategy which is being articulated for Africa. It is called An Agenda for Action for HIV/AIDS, and the most important part of it is to deal with the HIV/TB co-infections.

Turning to research and based on the excellent presentations this afternoon, there are three areas where the bank would, without other partners, would like to join hands and do some of the vital research that is needed.

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The first one would be clinical: New ways to optimize the management of co-infected individuals, when to start end-stage therapies within the new context of emergent XDR-TB, developmental new drugs and diagnostics. This is an area where we would be more than happy to join hands with our partners.

The second area would be epidemiology. How does HIV drive the TB epidemic and vice versa, and what are the population level impacts of AIDS treatment on incident TB? And finally on the operation of research, how to implement TB and HIV programs to ensure that they strengthen and synergize and ensure appropriate and prioritized and locational resources to health systems and co-design and co-implement TB and HIV programs to force a true continuum of care.

So these would be the areas that we would look to the Global Fund, WHO, UN AIDS, work with closely. And I'll stop here. Thank you.

DIANE HAVLIR, M.D.: Thank you. Thank you. Our next panelist is Dr. Charles Mongonie from EDCDP.

DR. CHARLES MONGONIE: Thank you very much.

First of all, I'd like to start by saying what is it TB is and then briefly how do we KO the activities.

EDCDP is a European co-ministries [inaudible] in Africa through the reduction of poverty-related diseases of HIV/AIDS, malaria, HIV [cough]. The aim of the program is to integrate

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the European Nation of Programs of these three diseases, meant to work in partnership with African governments as well as third parties. The integration of the European National programs aims at creating synergy among the European scientists who are working with their African counterparts. In the past, there was a lot of fragmentation in many of the programs being carried between the North and the South and the involvement of the African partners is mainly to instigate and create ownership of the problem, as well as the agenda itself. Again, in the past, quite often, things were always top/bottom, partners in Europe decide to a program and then they have, in the past, they would have had a counterpart in South, mainly based on former colonial ties, like we have [inaudible] in UK working with particular institutes in Africa, institutes in France working with particular institutes in Africa and we are trying, very much not, to remove those gaps, but working with the set partners is to add value and by set partners here, I mean, public/private partnerships for productive global partnerships, [inaudible] agencies, as well as other interest in the North.

Recently, the approach of EDCDP has changed a bit where we now are basing clinicalal trials, is the main vehicle of carrying out our activities and personnel development and networking is added value. We always talk about doing

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[inaudible] clinical trials in developing [inaudible], but quite often, the capacity to do the clinical trials tend to lack more in terms of personnel as well as enabling environment. Things like, for instance, sound ethical review and [inaudible] framework. The aim of the program is not only to enable [misspelled?] clinical trials, but to be the capacity to conduct these clinical trials as well as to improve the environment for conducting these clinical trials so that the clinical trials are conducted on the best practices and clinically is internationally [inaudible] in the world.

Our method is now, again, usually a bottom-up. In other words, before we conduct clinical trials or before we decide to put up a call, we call a stakeholders' meeting, with all players, people from African Communities, [inaudible] communities, policy makers, people in the pertinent industries as well as product development partnerships, will stick together in our, usually one-day type of meeting, and thrash out the common areas.

In the field of tuberculosis and HIV/AIDS, we have four major stakeholders' meetings recently, one on HIV vaccines, another one on HIV treatment, and one on TB treatment and another one on HIV vaccines.

Based on this, would you say what are the molecules which are in the pipeline? What are the status which we think

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are likely to benefit the scientists? And together after deciding, then we put up goals. For the three diseases which we had put up all the TB vaccines on the 6th of July, this is open and will remain open until the 19th of November. There was another call on TB treatment. This will be put up on the 5th of August, in two weeks' time, and will remain open until September of this year.

For HIV treatment and HIV vaccines, we will put up calls early next year, hopefully sometime in February.

Besides this direct HIV- and TB-related activities, we also support clinical trials in general and one of the modes we're going to do is put up an branch, again in August, the 5th of August, to conduct or to set up centers of excellence of conducting clinical trials on four main regions in Africa that is Eastern, Southern, Western and Central.

This, we've noticed, is important because there are some areas that tend to be very weak. If you look at most of the activities on clinical trials that are conducted, they are mostly in the Southern part and the Eastern part and some areas in the Western and hardly anything in the center of Africa, for instance.

Take an example of what was presented this morning on tuberculosis and HIV co-infections, you will realize most of the work seem to come from Southern Africa. This is not just

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because the body of the problem is there, but also because the expertise tend to be there and tend to like elsewhere. This is where we strengthen the South/North networking and the mentorships in our programs.

The other activities which, as I said, tend to let the ethics and [inaudible] framework, and we look to do this with other partners, in particular, the ethics work we are doing with WHO, but we are also doing [inaudible] with other agencies, including the European Medicine agencies here as well as WHO again there.

In summary, besides putting up funds for conducting clinical trials, we strongly support the improvement of capacity and we are looking to do this a lot with third parties and especially from the Northern part of the world. Thanks.

DIANE HAVLIR, M.D.: Thank you, Dr. Mangonie. I would really like to request the other panelists to restrict themselves to three minutes so that we have a little bit time left over for some discussion. I'd like to invite Dr. Renee Ritson from the Gates Foundations.

RENEE RITSON: Thank you. Before I start my comments about the Gates Foundation, I first want to acknowledge the passing of George Comstock this week. Dr. Comstock was an American Epidemiologist who spent his life working on tuberculosis and had given us many pieces of information,

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specifically about [inaudible] therapy as well as PgG. He was over 90 years old and he had spent his entire life on TB, so I just wanted to acknowledge his work and his dedication to TB.

I think the speakers have emphasized the importance of TB and HIV and once again, brought home the point of, it's not a question of if people with HIV in Africa will get TB, but when people in Africa with HIV will get TB and the looming and the terrible problem that this is. The Gates foundation certainly acknowledges the importance of TB in HIV infection as a very important part of both HIV and TB. To date, the foundations has funded the Create Project through John Hopkins, which is headed by Dr. Dick Chason [inaudible] and Gavin Churchyard [inaudible] is also a part of that, he is here in the audience, looking at different methods of dealing with HIV and TB. I want to reiterate what Michelle has said and that is the incredible importance of civil society in making sure that policy makers and stakeholders are well aware of this. There is some support to civil society activates, Mark Carrington [inaudible] is one of the people that has worked very, very hard and the Gates foundations, it is a pleasure for the Gates foundation to be working with him.

More basic problems in TB certainly relate to the problem of TB and HIV and certainly drug resistant TB and that is that there needs to be a better diagnostic, full stop. It

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needs to happen. Current diagnostic methods are non sufficient and we need to work on doing that. Also, there needs to be better treatments that can both shorten the duration of treatment and also offer treatment to resistance TB. The foundation is also dedicated to delivering that.

The final think, is, of course, the vaccines. The best way to prevent any infectious disease is to have vaccine and the foundation is solely dedicated large amounts of resources to looking at the development of TB vaccines. Thank you.

DIANE HAVLIR, M.D.: Thank you. I'd like to invite Dr. Michelle Zawaba, who is deputy director of the UN needs.

MICHELLE ZAWABA: Thank you very much. Thanks to invite us to be part of this panel. Let me start by just reflecting on experience we had with HIV/AIDS. If we take one minute and we try to look back, we will find clearly that from a nation of powerful activism, political advocacy and commitment from, I can even say pharmaceutical industry, [inaudible] help us to really find a test which we could carry out, in some cases, at home levels. In more than [inaudible] of drugs with different mode of action. But if you take one minute and compare that to the TB situation, all our TB drugs, diagnostics and vaccines date from the last century, I can even say the century before that. Let us be frank, have you presenting the different results, it is very difficult to

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manage the response to TB with the current level of research. The lack of progress is not surprising if you look at really, what type of assessment is made. The US. .National Institute for Health spent almost \$3 billion in HIV aids when we can say that HIV/AIDS [inaudible], compared to TB, less than \$150 million. It is clear that if we maintain the same level of assessment, it will be very difficult to make the difference and to find those diagnostic and different tests which would be certainly most [inaudible] to respond quickly to this major challenge. We should not forget that one-third of the 40 million people who are also infected with the TB activists who are already talking about the need of five, an increase by five fold. We need probably \$2 billion annually if we want to make a quick difference.

I don't want to spend too much time on that, but I want to come back to what we in AIDS could do. Or are doing. First is to build on experience to built with civilian society activism and use their expertise and their knowledge to suddenly clear a momentum around TB advocacy. Build up their capacity to increase better demand for TB prevention and [inaudible].

The last board of HIV/AIDS called on the United States to invest more in TB and we are convinced that we are not talking about different agenda, we are talking about one agenda

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HIV and TB. And more and more we will enforce our collaboration with different partners in the field and particularly with global funding. We are working closely together, WHO, we have [inaudible] and staff now working in UN aids [inaudible] with us to help us certainly better strategize with [inaudible] we're investing in this area. I will stop here.

DIANA HAVLIR: Thank you. Dr. Kevin De Cock, who's the head of the HIV division at WHO.

KEVIN DE COCK: Thank you very much. Good afternoon, colleagues. I'll try to keep my comments brief and try to emphasize some of the public health issues and questions that have been raised from this useful discussion. Obviously, there is no one agency that can address all these issues, the need and the performance of partnerships have been demonstrated in the discussions. At WHO, there's at least three departments that work on some of these aspects of TB, the HIV department, the stop TB department and the TDR, the tropical diseases research program. I think a useful way of looking at the whole issue, one has to look at the whole issue, and by directional sense, looking at HIV from the perspective of the community, dealing with TB and the prospective of the TB patients and the other way around, looking at tuberculosis from the perspective of the HIV community and the HIV infected patient. This

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important question that has come up several times as to what extend the approach that both diseases should be integrated or coordinated, that's what's been long talking about that, but it's the point I want to make. That should actually be [inaudible] to being examined in a research prospective in a way that brings integrated care to where the patient actually prevents and maintains the expertise that's very necessary for both diseases without diluting it.

From the TB perspective, some of the important issues are, testing every patient for HIV. If the patient is positive, both patients with TB and suspected TB, delivering with co-trimoxinal prophylaxis if the patient is HIV infected and then delivering or referring infected individuals for ART. In all of that, I think we've done moderately well and WHO, which whose at the global level, one of whose main tasks is that the delivery of guidance and technical guidance over the last year, I think important guidelines have been published on co-trinominal prophylaxis and AIT in adolescents and adults, published last August and more recently in May of this year, on provider initiated testing and counseling and health care settings. The delivery of HIV testing in health care settings and the importance of that kind of advice is not that other people cannot give it or already know it, but that it's sort of a benchmark that's set at the global level that becomes a

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minimum standard of practice and in some instances a permission to do things that had previously had not been done.

I won't comment on the many individual research questions that have been raised, but I think a question that does have to need more emphasis, that I don't think was discussed, was how to prevent recurrence in the HIV infected patients, which remain substantial even in patients on antiretroviral therapy. From the HIV perspective, I think we've done less well. Important issues that have been raised are screening HIV infected patients for active tuberculosis, obviously treating them if they have active TB, the issue of preventative therapy and that of infection control. Ways of looking at this are to discuss what new tools we need and how to better use currently available tools. As far as new tools are concerned, I do see somewhat of an analogy between HIV and TB, the endless discussions about an HIV vaccine has been going on for, I think, as long as the endless quest for better drugs tuberculosis shorter regimens and better diagnostics. It is frustrating how slow progress has been in these areas, but they are obviously immensely important.

I do think we still need deeper thinking and more imaginative thinking leading to asking the right questions. I've was stricken by Steven Long's presentation, the severity of the problem in South Africa and southern Africa is quite

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unique. It is a perfect storm, if you will, of tuberculosis and HIV coming together. I cannot help but feel that any of these current approaches that we've been talking about actually are not going to do it and that we need to be asking some kind of question about what kind of population level intervention could be assessed, either for people known to be HIV-infected, focusing on them, or even more broadly at a community level.

I want to make a comment, generic comment, also, about the missed opportunities in my opinion of the current scale up of antiretroviral therapy. The huge resources going into programmatic scale up, particularly in Africa are sometimes unguided as far as knowledge is concerned and I think we're missing opportunities for research piggybacked onto that programmatic expansion including through the use of large simple trials addressing very fundamental questions such as, for example, the still unaddressed issue of when to start antiretroviral therapy in general.

I think one of the biggest concerns in all of this, raised today by Jerry Friedland, has got to be the implications of MDR and XDR on the HIV epidemic in Africa. Highlighted with South Africa, but we don't really know what's going on elsewhere terribly well. Sort of, the potential to have sort of New York City in the south, if you will. The impressive situation in New York City in the late 1980s and early '0s

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could be playing out unrecognized in Southern Africa and the implications of XDR really are extremely serious. Perhaps the worst potential being the concept developing that actually it's dangerous to look after patients with HIV or tuberculosis, not because you yourself might get tuberculosis, but because you as a health care worker might actually get incurable tuberculosis. I think that's an extremely serious issue we need to be thinking about. It also raises the very important issues of health care system strengthening, particularly laboratory capacity on the African continent on the face of this emerging threat in a way that we haven't discussed seriously up until now. I think I'll stop because of time, I'll stop my comments there. Thank you.

DIANE HAVLIR, M.D.: Thank you Dr. De Cock. I invite Dr. Barbara Long from the NIH.

DR. BARBARA LONG: Thank you very much. I'll just make a few brief remarks. I'm here representing the US National Institute of Health, the NIH, which is part of our broader department of health and human services and NIH really is the primary research component of that department and we have been supporting continued support of broad and comprehensive research portfolio on tuberculosis and to a larger extent, a portfolio on HIV/AIDS research. We've been working for some time, as you've heard today, on several studies which are

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randomized controlled trials which are ongoing and hopefully we will begin to address the HIV/TB co-infection issues.

Primarily supportive HIV TB is primarily supported through the division of AIDS and [inaudible] although we have within the broader scope of NIH, other institutes, such as the National Institute on Child Health and Development; the National Institute of Heart Lung and Blood institute; as well as the Fogarty [inaudible] International Center, all of which has begun to work together to try to improve our capacity and our level of funding of HIV/TB. As a piece of that, the National Institute of Allergen and Infectious Diseases has recently published online a comprehensive research addenda for MDR/XDR TB and have identified several major areas. This isn't really a call with funds allocated already for it, but it's rather a discussion within the experts within our institute of where the gaps are and where additional funds would be needed to support new emerging areas. We've identified the very much, the same areas that we've heard about today. Primarily in new TB diagnostics, TB/HIV diagnostics, improving therapy for all forms of TB, better understanding of basic biology and immunology of TB and TB/HIV infected individuals studying though epidemiology, the MDR/XDR epidemic as it effects HIV populations, enhancing the clinical management of drug

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resistance in people with and without HIV/AIDS and improving TB prevention straggles including new vaccines.

This agenda was presented at our research counsel of May of 2007 and there have been some activities in the U.S. government in the congressional arena for identifying additional support for NIH which we have not yet realized. But, despite that, I would say that we are very open and invite these kinds of research questions to be submitted as investigator initiated requests for support through grants within our current funding system and we encourage research studies that will be broad in the sense of not only understanding basic biology but also approaching better management in other sites around the world.

We look forward to collaborating with our sister funding agencies in other nations and in other multinational organizations in hope that we can bring things together better to coordinate our research activities such as our recently funded large clinical trials networks, which have broad activities in many countries effective by the HIV epidemic. We've been working closely with PEPFAR [inaudible] with some of the Gates Funded Public/Private Partnerships for we've increased our portfolio in multidrug-resistant TB through our bio-defense initiatives, stop TB partnership is an activity that we continue to be active in and as part of the, as was

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mentioned with the implementation of assistance though [inaudible] through PEPFAR, there certainly are opportunities for the bottom up applications of countries to propose studies that could be considered public health evaluations that we are emphasizing this year through PEPFAR support for HIV/TB in particular. This would be an important time with the upcoming country operating plans for PEPFAR for our countries to, in the implementing partners to propose activities in some of these research areas that I've mentioned. I'd like to also mention that the Fogerty International Center is looking at some imaginative ways to improving capacity to training and Dr. Gene McDermick, who's where from Fogerty, could speak more about that if anyone is interested afterwards.

Lastly, the National Institute of Child Health and Development is considering having a request for proposals fairly soon which would deal with childhood HIV/TB both in the area of treatment and diagnosis. I guess my main message is NIH wants to continue to play in the world stage in close collaboration with our partners, the ANRS, the Gates Funded Initiatives, Create, as closely as possible and to encourage investigators to please submit proposals on the many of these important questions and do it through our normal granting mechanisms three times a year. We would very much like to receive more. Thank you.

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DIANE HAVLIR, M.D.: Our final panelist is Dr. Xavier Blanc from NRS.

XAVIER BLANC: Thanks a lot. First of all, I'd like to say that I'm here because the director of NRS [inaudible] with not arrive in Sidney until later this afternoon, so he asked me to [inaudible] and to tell you key facts about NRS. NRS is a French National Agency for research on HIV/AIDS and hepatitis. Ninety-seven-percent of it's budget comes from public responses. Only 3-percent from private companies. Ninety-percent of the funds directly support with such projects. It's divided into six sections, basic research; clinical research; social science vaccines; research in low income countries, developing countries; and research on hepatitis. To get funded, it's basically a bottom-up process, there are two goals for proposal each year and you, through the 15th of March through the 15th of September all the project are [inaudible] by independent panel of experts then the answers are given at the end of June and at the end of December each year. NRS works in eight sites all over the world. Five in Africa, [inaudible], recently opened in April of 2007, two sites in southeast Asian, Vietnam and Cambodia and one site in Brazil. This involves several researchers and the reason I remember [inaudible] and local people works long time ago. Then the sites can propose applications to get funded. Basically, even if you don't

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belong to any sites, you can submit application to NRS, given the fact that this research is linked with a French team, working in low income country. [Inaudible] there is a big study that's call [inaudible] and it's the currently [inaudible] is 3.4 million euros, but you should multiply that by 2 or 2.5 to add the real cost of the project if you include the salaries and so on. So, basically two [inaudible] per year, 15th of March and 15th of September. Applications in English or French, but you need to involve French researchers working in low income countries to get funded. There will be a top/bottom meeting for TB and AIDS probably at the end of this year.

[END RECORDING]