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Looking to the Future in HIV and TB
Kaiser Family Foundation
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DIANE HAVLIR: It is really my great pleasure to introduce the co-moderator of this session who really needs little introduction to this audience, Mr. Mark Harrington, who is a Founder of the Treatment Action Group, and how is a pioneer in HIV activism, TB activism, and HIV and TB activism. When we think about social movements, AIDS is a social movement, and when you think about Mark Harrington, every social movement needs a Mark Harrington, because when you see what Mark has done for us it's really, simply extraordinary [applause]. Without further ado, Mark.

MARK HARRINGTON: Diane, thank you so much for that very, very kind introduction. Every social movement needs a Diane Havlir [applause], an Allison Grant, and Richard Chaisson, a Haileyesus Getahun, a Tom Evans, and a Whoopi Goldberg [laughter]. I'm really proud and excited that all of you came to this session on the last day of this very exciting conference, where we're at the turning point of so many of the work we've down.

We started talking this week about entering the cure era of HIV. Imagine being able to actually cure the disease for all 34 million people would take us away from the treatment mortgage where all of us have to be on triple therapy for life. Guess what we've been in the TB cure era since before I was born and the same number of people die from TB every year as

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die from this incurable HIV, and so some of us for the last 10 years have been trying to put together the lessons of the two epidemics, and the services, and the activism, and the science, and the political will. To get to zero new infections, zero death, and zero suffering and stigma for HIV, but also zero deaths, zero suffering, and zero stigma for tuberculosis.

I'm gonna talk about three particular ways that we can get there. First way is to focus on kids with TB. Every kid that gets infected with TB got infected usually at school or their family, that means every time they got infected somebody missed treatment of their mother, their father, or someone in their house, or someone in their school. Every single one of those pediatric cases can be prevented, treated, and cured, but for the last 50 years the world's TB programs ignored children, that has to change and it has to change now [applause].

Imagine if we'd ignored HIV in children, not only would we not have drugs and treatments for millions of kids around the world with HIV, but we also wouldn't have prevention of mother to child transmission, which led to treatment in Africa and globally, and so we wouldn't have eight million people on treatment if we hadn't prioritized children in the early days.

We need to put a priority on kids with TB and get their infection rate down to zero. We won't be able to do that unless we have a point of care, cheap, accessible diagnostic

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test that can detect tuberculosis in every person that's living with it [applause].

We need to spend $400 million a year on TB diagnostics research, and we're only spending about 30 million. We call on global leaders to fund a research to end the epidemic.

The third thing, which is really what this whole panel is about today is the TB/HIV program integration that we've seen over the last 10 years that every single speaker is gonna talk about is a beautiful model of working together, north and south, men and women, adults and kids, activists and scientists, policy makers and you'll hear later that doing this program integration not only set a new model for global health, which is that you work across disease lines, but has also saved more than a million lives of people living with HIV who have not died of TB, and of people with TB and HIV who have not died from HIV, cause they've gotten antiretrovirals through the kinds of studies that Diane has led.

I'm really excited and it's appropriate to have the first speaker be Allison Grant from the London School of Tropical Medicine and Hygiene in the United Kingdom.

She's been a leader and an inspiration to a whole generation of TB researchers all over the world with her powerful research insights and study designs of studies of drugs to prevent tuberculosis in people with HIV, but more than that in adopting a [inaudible] approach from HIV, she's gonna

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talk about combination TB for prevention strategies. And just as with HIV there's no magic single approach for prevention that's gonna work in all cases, so in TB we need to take every tool that we have in the tool kit and put them all together, so we could prevent every single case of this disease, which is both treatable and curable, so Allison.

ALLISON GRANT: Thanks very much, Mark, for that very kind introduction, and thank you it's a great honor to be asked to talk today.

I'm going to show you first of all a slide representing out TB circulates in the community. The person at the top of the slide has mycobacterium in the sputum, as it's transmitted to other people in the community, and most of those people will never go on to develop TB in their lifetime, but a few will, and people who have HIV are at extraordinary much higher risk of developing active disease and moving rapidly from infection to active disease. If we want to intervene to break the cycle, first of all we need to think about how we can reduce transmission to prevent new infections and secondly how we can, among people who already have latent TB infection, how we can prevent them developing active disease.

The priority depends on where we, since this is the Grand Canyon, and in settings like U.S., properly TB is a rare disease and TB transmissions are a rare event, so the focus of TB prevention is on people who have latent TB infection and

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preventing them from developing active disease. The standard of care for this is isoniazid preventive therapy or IPT.

We have lots of evidence to know that, that works, so for example amongst people with HIV in clinical trials we know that overall people receiving IPT have a one-third reduction in their risk of going on to develop active TB.

If they have a positive tuberculin skin test, they've got a two-thirds reduction in their risk of developing active TB, but in order to do that they have to take IPT for six to nine months, that's a long time and retention in a long care program like that is typically quite difficult and completion rates are poor, so shorter regimens would be preferable if they were safe and effective.

At the end of last year it was exciting to see the results of the PREVENT TB trial, which tested a novel TB preventive therapy regimen of Rifapentine plus Isoniazid given weekly, directly observed for three months, compared with Isoniazid for nine months. This study was carried out primarily in the U.S. and Canada, and relatively few people with HIV were enrolled in that study.

In terms of the efficacy, you can see in the red line at the bottom here that people in the Rifapentine Isoniazid arm, that arm was non-inferior to the standard of care of Isoniazid, so that's very encouraging. However as I mentioned not very many people with HIV were enrolled to this study, so

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enrollment was continued to boost the numbers of people with HIV, and Tim Sterling at this meeting presented data on tolerability of this new regimen amongst people with HIV.

Rifapentine interacts with antiretroviral therapy, particularly with protease inhibitors, so people entering the study couldn't be taking antiretrovirals for the first time, two days, and their median CD4 count was relatively high at around 500. What you can see is that in terms of the adverse effects, Rifapentine broadly was certainly no worse than Isoniazid, so that's encouraging news in terms of tolerability, and we're waiting there for data on efficacy which are due at the end of next year.

There are other shorter preventive therapy regimens currently under investigation, four months of Rifapentine as mono therapy is one, and then another ultra short course regimen of Rifapentine plus Isoniazid given daily for one month, both of those studies currently underway. Turning now to settings of high TB transmission, so here the focus has traditionally been eh person who's got infectious TB. Here treatment as prevention is very old news, it's not new for people with TB, we've been doing this for decades.

Thinking also about preventing transmission. We do need to think about places where we may not identify a person who's got infectious TB, and people are at high risk, and that's particularly in health care settings. I really just

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want to mention TB infection control, particularly in healthcare settings, as an area where it's very important for TB prevention, and I think still it doesn't get enough attention.

TB as we know is a disease which develops gradually, and people can remain infectious for relatively long periods before treatment is started. Anything that we can do that gets a person on to TB treatment earlier, represents prevention of TB by reduction of the duration of infectiousness.

Here I've tried to represent the pathway that the person with TB has to take and all the steps that they have to go through in order to get on appropriate treatment, and to be cured of that TB. [inaudible] is a straight line, in reality it's very much not a straight line, it's a very [inaudible] root for loss of people, often they will present several times with symptoms suggesting TB before they get an appropriate test, and even when they get an appropriate test then they may have to wait potentially a very long time before they get test result.

Anything that we can do which for a starter reduces the turnaround time on TB testing, it will reduce the duration of infectiousness and that's good for TB prevention. That's Dick Chaisson's talk and I'm not going to talk about that anymore, but what I do just want to mention is something slightly downstream of that, so we tend to assume, I think, that a

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positive test result leads to a person's starting treatment, and that should of course be the case, but it isn't always.

In the context of the South African goldmines in the Thibela TB study we looked at this and what we found to our surprise was that people with the median time between a TB test being sent and the person starting treatment, if they sputum smear positive was about 12 days, not so bad, but if they were sputum culture positive and smear negative the median time to treat was five months, which is really a long time.

If you look at those curves going out you'll see that quite a substantial number of people never started treatment at all, so no matter what the diagnostic is that we use, we do have to be sure if we're gonna get the best benefit from it, we need to be sure that a positive test result leads to appropriate treatment promptly.

We could perhaps be even better if we could speed up a TB test getting sent, and this was the premise of the ZAMSTAR study, which was a study in South Africa, in Zambia in 24 communities, where they were investigating whether getting TB tests sent earlier would improve TB control. There were two interventions, one was enhanced case finding, which involved mobilizing communities, encouraging people with symptoms to present, and bring a sputum for examination, facilitating that and making sure they got their results promptly.

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The second intervention was in households using a person with TB as an entry point for offering testing for both TB and HIV to the entire household, followed by referral for treatment and care. What they found was that although the enhanced case finding component didn't seem to make a difference, the household intervention did have an effect on prevalence at community level, reducing it by 18-percent, and reducing transmission measured in children by about half. I think it's very encouraging that by promoting earlier testing for TB we can make a difference potentially to TB control at population level.

Moving away from reduction of transmission and thinking now about preventing reactivation. As in low transmission settings, a shorter regimen would be desirable for all the same reasons, but early work on isoniazid preventive therapy suggested that a six months course of isoniazid preventive therapy perhaps didn't last for very long and only had benefit for about two years, so we have to ask ourselves the question, is longer better?

This was addressed by two studies which were reported last year, firstly one in Botswana which compared six months of isoniazid to 36 months of isoniazid. This was amongst people with HIV regardless of their skin test status, and what they found is that while people were taking the 36 months of isoniazid, they had a reduction in TB incidence, compared to

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the people who only took six months of isoniazid of 46-percent, so that's an impressive reduction.

However in further results which were presented earlier this year at Croy [misspelled?], presenting results after the end of the isoniazid, what they found was that TB incidence rapidly returned to the previous level, so although the 36 months of isoniazid worked will while people were taking it, after people stopped taking it that effect went away.

In [inaudible] in South Africa, similarly a study led by Neil Martinson compared six months of isoniazid to continuous isoniazid, but in addition have two novel preventive therapy arms, one with Rifampin and Isoniazid, and the other with that Rifapentine isoniazid weekly, described earlier.

Briefly in terms of the primary outcome which was tuberculosis or death, there was nothing to choose between those four arms, but in an as treated analysis, if you look at the line at the bottom, that solid black line, that shows TB incidence among people in the continuous IPT arm while they were actually taking it.

So, again we've got evidence that isoniazid preventive therapy works while you're taking. We've got further data relevant to this from the Thibela TB, so this was a study trying to improve TB control in South African gold mines. There we've got a really extraordinary epidemic of TB which is fueled partly by high HIV prevalence that's super imposed on a

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background of silica dust disease, both of these being very powerful risk factor for TB. And despite conventional control strategies, TB case notifications got as high as 5,000 per 100,000 per year, extraordinarily high.

We tested a novel strategy of community wide IPT, just to explain what I mean by that, usually we give IPT in a targeted way, so people who are identified at being high risk of developing active TB receive IPT. In community wide IPT, this is relevant in populations where everybody is at very high risk of TB. And the strategy here is that we offer screening for active TB to everybody in the entire community.

People who have active TB are referred for treatment, people who don't have active TB are treated for latent infection. The idea is that everybody in the entire community gets either treatment for active disease or treatment for latent infection at the same time, and by doing that you should be able to rapidly bring down TB case notifications, that was the idea.

This was a cluster randomized trial in 15 gold mines in South Africa with approximately 80,000 people. What we found however was that there was no impact of this intervention on TB prevalence population level. To try to understand that Katherine Fielding did an individual level analysis looking at people who were in the baseline survey study, so about 15,000 people.

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She looked at 6,000 people who were in the baseline survey in the control cluster, so whether it was no IPT, and about 5,000 people in the intervention clusters who actually started IPT in the context of the study. She compared TB incidence in those two cohorts, and what we found was that amongst the people who were in the intervention clusters actually started IPT there was a 63-percent reduction in TB incidence during the nine months of the intervention, but after the intervention that effect went away pretty much immediately.

Again, we've got really very consistent data suggesting that IPT works while you're taking it, but unfortunately it doesn't seem to have a durable affect after you stop, so why is that? Is it the most obvious explanation, very high rates of TB re-infection, this is very difficult to measure, but certainly that would be consistent with molecular epidemiology data, suggesting that people with HIV getting recurrent tuberculosis primarily get that as a consequence of re-infection?

And that would certainly explain for example the [inaudible] results where even in the groups who were getting potential better, treatment for latent infection with Rifampin containing regimen doesn't seem to have helped, because as soon as they stopped they just got re-infected and developed disease again.

However I don't think we understand everything that there is to understand about the epidemiology of TB in these

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settings still. I want to illustrate that with some of the results from the Botswana study, as you know probably know the results were very different amongst people who were tuberculin skin test positive and negative, and the people who were tuberculin skin test negative at the start of the study didn't benefit from continuous IPT.

What I think is interesting though is how is it that TB incidence receives so low in the placebo arm of people who are TST negative, even though their TST result was some years ago, if most TB is due to re-infection it's a little bit difficult to really understand that, so I think there's still more to understand.

Another potential contributor could be that IPT just isn't the right drug, isoniazid is not very good at curing latent infection, again this is very difficult to measure in people, but there are some data from mouse models that are helpful. If you look at the figure on the right hand side this is illustrating the duration of various regimens and anti-tuberculosis drugs required to prevent the development of active disease in a mouse model of latent infection.

What you can see in the top bar is that even six months of isoniazid is not enough to prevent relapse, where as with some of the newer regimens and in particular that orange one down at the bottom, that's TMC207. They seem to have much more activity against latent infection, and I think that's raising

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very exciting possibilities that some of the new TB drugs in the pipeline will be active not only against active tuberculosis, but also will be effective in the treatment of latent infection.

What are the implications of this limited durability of IPT. Well I think mostly it's re-infection, clearly the priority is to reduce TB transmission. If the problem is that IPT is not quite the right drug then we need better preventive therapy regimens. I suspect there's probably a bit of both things going on, but either way the data do seem to suggest that while people are taking IPT they are protected, so perhaps continuous IPT is the way forward.

Thinking again about preventing reactivation of latent infection we also need to think about addressing susceptibility and here particularly we need to think about antiretroviral therapy, so I've got lots of good data in this matter, an analysis was published this week looking at the effective antiretroviral therapy in preventing TB, showing that it has a 65-percent results and 65-percent reduction in TB overall.

That's great, but I would like to argue that ART is necessary, but it is not sufficient, and that's illustrated by this study here from Ken Kohortz [misspelled?] in Cape Town. If you look at the bar on the left hand side that you can see that amongst people who were taking long term antiretrovirals, that's for more than five years, TB incidence in that group was

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still five per 100 person years, which is still unacceptably high, so I think ART alone is not going to do it.

What about if we add antiretrovirals to IPT, well observational data has suggested that a combination of the two is better than either alone, and these are data from the trio study, but it was great yesterday to hear in a late breaker from Layla Rangarka [misspelled?], and news about a randomized control trial investigating the same issue, and so this was a study where people either starting ART or already on ART was randomized to received 12 months of isoniazid or placebo, and what she found was that there was a 37-percent reduction in TB incidence amongst people who are receiving both IPT and ART. It's great to see these data confirmed with a robust study design.

Still I think we potentially need to do even more than that, and I want to just come back to the Thibela TB study which is an extreme example of a TB epidemic, where community wide IPT did not improve TB control in the gold mines.

We asked our mathematical modelers what it was going to take and we gave them a little menu of things that they could model, and we asked them to go away and go figure, and what they came back with was this, so they said, well if you tighten up your systems and you make sure that people start treatment promptly, you'll get a bit of an effect, a nice effect just by doing that.

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If you use more sensitive diagnostics and screen people regularly you'll get an effect from that. In this particular population HIV is a very strong driver, and so by maximizing ART coverage, so for everybody who's HIV positive regardless of CD4 you'll get quite a big effect from that, but you can get an additional effect as well by optimizing preventive therapy, so giving continuous IPT to people who are HIV positive.

I think that leads us to the idea that perhaps what we really need is combination TB prevention, so not just ART, not just ART plus IPT, but other things as well will contribute, and if we do all of these things and all of these things are achievable now, we could really start to make a big difference in terms of TB prevention.

In conclusion, firstly I think the HIV message of know your epidemic, know your response applies equally well to TB. In settings where transmission is rare we've got Rifapentine and Isoniazid looking very promising as a simpler and shorter regiment, and looking forward – enthusiastically telling some efficacy data for people with HIV.

In high transmission settings I think what's new is increasing evidence to suggest that IPT has limited durability, leading us to the thought that really we need to very seriously consider continuous IPT for people with HIV, but more broadly than that, I think we need to think beyond just antiretrovirals and optimizing TB preventive therapy, but I think we need to

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think about a combination approach. Yes, definitely those two things, but also thinking about can we use better diagnostics to provider earlier treatment, and can we also make sure that our systems are supporting all of these new diagnostics, so that we've minimized treatment delay.

I'd like to thank many people who helped me with slides, and ideas, and discussion. I'd like to thank our funders, and I'd like to thank you very much for your attention [applause].

MARK HARRINGTON: Thank you, Allison, for a great talk, which really sets up well the nest talk, which is on the promise and pitfalls of new TB diagnostics and drugs. I want to thank our next speaker, Dr. Richard Chaisson from Johns Hopkins University, because along with the next speaker after him, Haileyesus Getahun, and he's been a mentor to me in the often byzantine and bizarrely evidence resistance and reluctant to change worlds of TB research and policy that we spent the last decade transforming.

He leads the Hopkins Center for TB Research, the New Center for AIDS Research, The Create Consortium, and chairs the AIDS Clinical Trials Group, TB Transformational Science Group. Over to you, Dick.

RICHARD CHAISSON: Thanks very much, Mark, and thanks, Diane. Mark and Diane have given me a very ambitious agenda here this morning in light of their own ambition for this co-

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epidemic. I'm going to ask you to fasten your seat belts while I race through new TB diagnostics and drugs in the next 20 minutes.

When I was in training and many of you were in training, research on tuberculosis had evaporated. There was a false sense of optimism in the 1960s and 70s that TB was a done deal and there was no need to invest in it any further, and many of us had our training in the 1980s received no training in tuberculosis. This came back to bite us, but fortunately in the 1990s a return of science to tuberculosis, recruitment of investigators, including many working in HIV contributed to a really important upswing in discovering new products in the tuberculosis control arena.

Funding for tuberculosis research has increased dramatically in the last several years and this is Mark Harrington's tag pipeline report showing that there's now over $600 million a year in TB research, and as we'll discuss later, while this is great it is willfully in adequate. If you look on the bottom half of this slide you'll see where these funds are invested, and as Mark mentioned in his introductory talk, diagnostic investment has been very, very low, but in spite of the low level of investment in diagnostics the return has been spectacular.

I'd like to talk first about new TB diagnostics, so why do we need new TB diagnostics? The answer is really quite

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obvious, that is that many cases of tuberculosis are never diagnosed. There's a huge gap in case detection and in some parts of the world, such as Sub-Saharan Africa, fewer than half of all cases are diagnosed and most of these individuals with tuberculosis will go on to die without treatment, because of failed diagnosis.

Even in a fairly advanced country like Brazil diagnostics for TB have lagged behind other health interventions. And this data from HIV infected patients in Rio de Janeiro show that two-thirds of patients treated for TB didn't actually have a specific diagnosis with a chest x-ray being used in a little over half, and a clinical diagnosis in another 10-percent. The need of new diagnosis, diagnostic tools is severe.

There are a number of exciting new technologies that are coming online for tuberculosis diagnosis, and I'm not going to be able to talk about all of them, but I'll just quickly mention that new culture platforms which range from the highly sophisticated and technologically demanding like the MIGT system to rather simple approaches like MODS which can be done in laboratories that aren't as advanced as those that do MGIT, offer the opportunity for culturing of organisms where that hasn't previously been possible.

Nucleic acid amplification techniques are very important and I'll spend some time talking about that, as well

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as antigen detection methods. There's interest in cytokine expression and the use of interfere on gamma release assays has gained attention in the last several years, though has limited place in the diagnosis of active tuberculosis. Then there are some really new space age sorts of approaches with RNA transcriptional signatures using micro rays, detection and volatile compounds in the breath and other techniques such as novel imaging methodologies.

The development of new diagnostics that require sophisticated infrastructure in laboratories is a huge problem for the high burden countries, and these countries that are high burden for TB and HIV have very little existing infrastructure for tuberculosis laboratory diagnosis.

You can see that for tuberculosis culture the target that has been set by the WHO is one per five million people, and from drug susceptibility testing, one per 10 million people. With the exception of South Africa all of the high burden countries fall well short of this. To improve the laboratories in these countries however is an enormous investment in infrastructure, and approaches that can bypass, expensive new capital investment I think are the best way forward.

In the last several years there's really been a dramatic march of technology with the development of new tools, with this a modest investment in research that we saw earlier.

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And so LED microscopy, nucleic acid based detection of tuberculosis, and tuberculosis drug resistance with line probe assays, a truly revolutionary point of care test, the urine LAM dipstick that we heard from Anthony Harries this morning about, and then the GeneXpert MTB/RIF test which is a really transformational technology. Three of these four new technologies do not require a TB laboratory, and the urine LAM is a real point-of-care test.

We will take a minute to talk about the GeneXpert. The GeneXpert really is remarkable; it is a molecular biology laboratory in a cartridge. In a cartridge the size of an inkjet printer that costs actually half as much.

In this molecular biology laboratory in a cartridge, detection of tuberculosis using molecular beacons occurs in about 90 minutes, and detection of mutations conferring resistance to rifampin occurs at the same time so that at the end of an hour and a half, a readout is given that detects tuberculosis and rifampin-resistance, a surrogate for multi-drug resistant tuberculosis.

We know that from the initial analysis of this tool in the field that it is highly sensitive, it detects 90-percent of tuberculosis in individuals who are smear-positive or smear-negative with a single sample, but for smear negatives, one sample only gets 72-percent. For three samples, overall it detects 97-percent including 90-percent of those who are smear-

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negative, and in HIV infected individuals, overall three samples will detect 94-percent of tuberculosis. It has excellent specificity and excellent sensitivity for detection of rifampin resistance.

In a further analysis by Catharina Boehme from Find Diagnostics; on the left we see that the time to detection with the GeneXpert in the light purple is less than a day, of course, and it detects 90-percent of all tuberculosis, not as good as the MGIT, but certainly much more rapidly, and better than the sputum smear. On the right, we see the time to detection of rifampin resistance, and again, within hours, rifampin resistance is detected, 94-percent of it overall.

The uptake of GeneXpert has been swift and dramatic, and we see here that over 3,600 GeneXpert machines have been placed around the world in high-burden settings, and over 1 million cartridges have been purchased. Recently, UNITAID, the Stop TB Partnership, the WHO, the Gates Foundation and other partners came together with Cepheid the manufacturer and worked out arrangements to lower the price of these cartridges from $17 to $10 which will further advance their distribution and use in the field.

The uptake of GeneXpert has been most dramatic in South Africa, and this report from several months ago shows that over 350,000 individuals have been screened with a GeneXpert test. 58,000 cases of tuberculosis have been detected, about 16-

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percent of all patients screened using the GeneXpert. This compares to a 6-percent yield of the sputum AFE smear, so a very huge increase in case detection. And, 7-percent of these individuals have been found to have rifampin-resistant TB, so presumably multi-drug resistant tuberculosis.

The GeneXpert has applications outside of areas with a high-HIV/TB co-infection burden, and here is an example of the machine being used for active case finding amongst Tibetan refugees living in India who have a very high incidence of tuberculosis, higher than most African countries, and have a very high prevalence of multi-drug resistant TB, but are a small population, and using the GeneXpert at a local health facility outreach to monasteries, schools, and congregate living facilities has yielded a high return of new cases and an alarmingly high prevalence of multi-drug resistant TB, but these cases are now being detected more easily and readily because of this new technology.

The urine LAM test I mentioned is a test that has a specific niche, it is a test that is most appropriately used in patients with advanced HIV infection where the sensitivity is over 50-percent for detecting tuberculosis, at higher CD4 counts, however, the urine LAM antigen has fairly low sensitivity.

If you look at how this performs in hospitalized patients who are suspected of having tuberculosis, you can see

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that, overall, a sputum smear or LAM will identify 75-percent of these individuals as having tuberculosis. You can see that, overall, a sputum smear or LAM will identify 75-perecent of these individuals as having tuberculosis, of those who have it, and this is something that can be done on the same day.

The reason that the yield of the two is so high is that you can see down below that over half of patients with tuberculosis who are smear-negative are detected by the LAM antigen. So when this is targeted at patients with advanced HIV, this can be a rapid, inexpensive approach to diagnosis on the same day of the point of care.

Stephen Lawn and his colleagues recently showed that the urine LAM is actually more sensitive than the GeneXpert for detecting tuberculosis in urine specimens, and certainly it is much cheaper.

What are some of the pitfalls with new TB diagnostics? Delivery is a huge pitfall, how to operationalize them, have the laboratory and human resources needed to provide them to patients, the creation of log jams in laboratories and in clinics, the costs, the scalability, and finally the impact, will these make a difference?

If you look at how tuberculosis is detected in clinical services, you can see that there are an enormous number of opportunities to miss it, and most of these opportunities have nothing to do with the test, you can see in the middle panel,

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in the read, that the sensitivity of the test is but a small part of this cascade towards diagnosis.

Many other steps that involve delay in obtaining tests, delay in obtaining results, delay in delivering results to patients, and delay in initiation of care result in missed opportunities to cure tuberculosis.

We know that the GeneXpert is highly sensitive but it is not a perfect test, many patients who present with symptoms of tuberculosis might have an initial negative GeneXpert and what do we do with those GeneXpert negatives?

This very nice analysis by Sydney Rosen and colleagues presented a CROI shows that just repeating the GeneXpert will result in more patients being diagnosed, treated, and cured, at a lower cost, 11-percent lower total cost because of all of those missed opportunities that I showed on the previous slide. Doing a test that can be done at the time of a visit and with the results available within hours is preferable to doing a culture which will take days to weeks to return.

Data showed in this conference also shows that when properly applied to the right patient population, urine LAM can be a cost-effective approach. The left panel shows the impact in dallies averted if life expectancy of patients detected is 1.5 years, and on the right we see if their life expectancy is five years, we would expect that if their tuberculosis is diagnosed, their life expectancy would indeed improve because

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they would get treated and receive antiretroviral therapy which is sadly lacking for many such patients.

What about impact? This is a typical analysis of the impact of a new technology, it shows that when the Hain GenoType test was implemented in Kimberley, South Africa, the time to getting specimens into the laboratory analyzed and getting results available was dramatically increased.

But the question is: Does this make a difference to patients? What we see here is that even with a test that diagnoses MDR TB presumably within a day, it still took 62 days for patients to get started on MDR TB therapy on average, compared to 78 days for those in the era before the Hain test was available.

However, if you include the patients who were missed because the Hain test was not available in the pre-implementation period, you can see that in fact there is a dramatic impact on patients, and preliminary evidence that this affects survival as well. However, 62 days to treatment for MDR TB with a diagnostic test that gives results in a day is simply unacceptable.

We will quickly move on to new drugs for TB, and I think the rationale for this has already been stated quite well, so I will not linger. We clearly need new drugs for tuberculosis. The good news is that there is a pipeline, although the pipeline is not as full as we would like it to be,

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and of the drugs in phase III right now, only one is really a novel agent, the other two being fluoroquinolones, so we need to fill this pipeline a bit more.

The path to getting new TB drugs is long and arduous, you have to go through all of the development of the compounds, the toxicology and chemistry and formulation work, animal models to predict what outcomes in humans might be, phase I studies of pharmacology and antibacterial activity, and then finally, phase III clinical trials which take a long time to complete.

Traditionally, this approach has been done for each drug, and each drug takes a number of years to develop so that it is decades before a new regimen of tuberculosis drugs will come along.

The Global Alliance for TB Drug Development has recently proposed that we try to more efficiently do these by developing combinations of novel agents simultaneously rather than sequentially.

If you look at the history of moxifloxacin as a drug that has been developed to shorten treatment of tuberculosis, it has taken a decade and a half to go from a very strong animal evidence to clinical trials that will answer whether this indeed will shorten therapy, and we still have two more years to wait before we will get that news.

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There have been a couple of new drugs that we have heard about in the last several years that are extremely exciting and promising that have been, to this point, developed under the old paradigm, so bedaquiline or TMC207 and delamanid from Otsuka have been studied in placebo-controlled trials for patients with multi-drug resistant TB, and they both have a similar level of activity, sterilizing the sputum of just under 50-percent of patients at two months. But, this is a pathway that will not lead to new combinations any time soon if we do not change the paradigm.

Similarly, we saw yesterday at this conference in the late breakers, a new drug, an oxazolidinone, sutezolid, presented by Robert Wallace, that has good early bactericidal activity, and this is a drug that also is promising for development as part of a new regimen of TB drugs.

The Global Alliance's proposal is that we take our compound candidates, put them in a pool and study them as regimens rather than as individual drugs all the way to registration.

This approach was done recently in a mouse model by Eric Nuermberger at Johns Hopkins showed that the combination of the novel drug PAA24, moxifloxacin and pyrazinamide, shown in red, led to much faster reductions in bacterial load in the lungs of mice than the standard regimen of rifampin, isoniazid and pyrazinamide, suggesting that this would be a promising

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compound. Then studies in humans showed that indeed, this is the case, the PAA24, moxifloxacin and pyrazinamide regimen outperforming the standard four-drug regimen over 14 days, and this has led now to a clinical trial, with this combination, in phase II.

There are a number of pitfalls in development of new TB drugs, not the least of which is toxicity and dealing with drug-drug interactions, the need for large phase III studies because of the lack of endpoints, just to look at drug interactions, bedaquiline or TMC207 interacts with efavirenz in a way that is complex and involved a metabolite that may increase toxicity, so this is a challenge.

At this meeting, we saw data on delamanid that in fact it does not interact with tenofovir, lopinavir or ritonavir which is very promising news.

Surrogate endpoints in TB clinical trials have been developed over years, and we clearly need to do much better with these, we have EBA, time to positivity, and the two-month culture conversion, but these are not robust enough tools, and we need to develop better biomarkers for use in clinical trials.

To end, I am going to tell you that we need to fund the pipeline and develop new regimens that will work in all forms of TB including MDR, HIV-related TB, and in children, and we need to approach this as development of regimens, not

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individual drugs. We have to change the paradigm and focus on developing good drugs, not second-rate, second-line drugs, crappy drugs that we have dealt with for decades that you would not give your dog that you have to give your patient.

What does the future hold? I hope that in a few years, like with HIV, we will have simple guidelines for how to treat patients based on what we know about the mechanism of action of the drug, a list of agents in that class, and then guidelines for which patient population to give these drugs to. This is the hope for the future, but I think it is not too much of a hallucination.

Just to very briefly and hurriedly conclude, after a very long gap science has been applied to tuberculosis with great results, enormous progress with diagnostics, there are still major challenges with cost and implementation, a lot of potential for new TB drugs, but still a lot of challenges to overcome, and we have to focus on evaluating regimens. The pipeline needs to be filled, and we need more investment and commitment.

To end, we talked earlier today in the plenary about getting to zero, this is the campaign of the WHO and Stop TB Partnership, so how do we get to zero? I would like to suggest that one way to get to zero is to add a zero to the level of funding for TB drugs, vaccines and elimination, and if we add a zero, I think there is almost nothing we cannot do.

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Thanks to my collaborators, funders, and thanks to you for your attention.

DIANE HAVLER: It is my pleasure to introduce our next speaker, Haileyesus Getahun, Dr. Getahun is a coordinator of the Stop TB department of the WHO in Geneva, and the Secretariat of the Global TB/HIV Working Group that works on policy, program, and in advocacy agenda.

He is a tireless champion of HIV and TB and outstanding researcher, and in a recent modeling exercise, it was estimated that nearly 1 million lives had been saved as a result of some of the HIV/TB policies that he has championed. Today he is going to be tackling a new challenge for us which we need in HIV and TB, which is integrating HIV and TB delivery, models, results, and prospects.

HAILEYESUS GETAHUN: Thank you Diane for that introduction, and I would also like to thank the organizers for inviting me for this presentation, and I would like to start my presentation by giving a little bit of a perspective of the situation. This graph shows the progress we have witnessed over the last several years about HIV testing for TB patients.

As you can see on this graph shown in red, the global coverage of HIV testing for TB patients has been increasing dramatically that in 2011 we had 2.5 million TB patients, or 40-percent of all notified TB patients were tested for HIV. This progress as seen in the blue dotted line has been also

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very significant for Africa, that by the end of 2011, we had 70-percent of all TB patients in Africa were tested.

One of the main reasons why we are testing TB patients for HIV is really to ensure they have access to comprehensive HIV care, including ART.

When we look, the current range of antiretroviral treatment for TB patients in the same way we have seen progress, but WHO recommends ART for TB patients regardless of CD4 count for all TB patients, and this has to be all 100-percent. But as you can see from this graph, the global coverage by the end of 2011 was only 48-percent, and the performance in Africa was also below the average for the globe. This is not matching the HIV testing progress.

One of the reasons for this could be the mismatch between the availability of ART services and TB services. TB services are provided in a much more peripheral setup, while ARTs are still centralized and in district hospital levels. This graph shows the distribution of TB facilities in the red, and ART facilities in blue in the four African countries which have contributed to almost half of the global TB/HIV burden by the end of 2011. There are more TB facilities than ART facilities, and this is true for all of the regions in the world.

This is the TB/HIV policy which was first introduced in 2004 that the previous speakers also spoke about, and this

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policy has given the clear recommendations of what needs to be done to address the TB/HIV response, basically by providing three critical areas of activities. The first set of activities are to provide integrative TB and HIV services, and the second area of activities is to prevent TB among people living with HIV, which we call the Three Is for HIV/TB, and the last one is to mitigate the burden of HIV among TB patients.

In my few minutes for discussing the models, I will use the activities recommended in this activity.

What about the models that we know so far? The first model is what we call the referral. The referral can start either from the TB clinic site that TB Patients are referred into HIV clinic for HIV services, like HIV testing, HIV prevention, or ART, or it could be from the HIV site that patients are referred for TB screening, TB diagnosis, or TB treatment.

The next model is what we call partially integrated. This is introducing HIV services within the TB clinic or introducing TB services within the HIV clinic. The most common TB service that is integrated into HIV services is TB screening, while the most common HIV service integrated into TB clinics is HIV testing.

The last model is what we call one stop service, in which both TB and HIV services are provided in the same service, in the same clinic, by the same health worker or in

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adjacent rooms by swapping health workers. This is what we call the [inaudible] located or adjacent room or one stop model.

What about the results? In the next few slides I will use the national data that are coming from countries which are implementing these models. The first is the referral model, and India has been the most prominent country that has promoted the referral model for HIV/TB, and in this routine referral of TB patients for HIV testing into the HIV testing centers, and people living with HIV with TB symptoms were referred for TB screening.

When we look, the referral trend from TB clinic for HIV testing, as you can see there has been quite substantial increase, and by the end of 2011, 45-percent of all TB patients or more than 700,000 TB patients notified in India were tested for HIV.

When we look, the referral from the HIV side for TB screening, there has been increase, as it is shown in the red bars, and by the end of 2010, almost 8-percent of people living with HIV seen either in HIV testing or these services were with TB symptoms, and they were referred for TB diagnosis, and by the percentage in blue shows the proportion of referred patients who were diagnosed with TB.

Another model or experience from India actually showed how this three models can evolve into a much more and one-stop

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service. Kenya started their partial integration in early 2003/2004 was introducing HIV testing and [inaudible] TB screening into the HIV services and eventually by providing by bringing ART and other HIV services into the TB clinic and having one-stop services. Today in Kenya, 60-percent of TB/HIV services are provided in the one-stop services.

This is again to show the result of the mixed model from Kenya where the HIV testing of TB patients has increased, and by the end of 2011, 93-percent of TB patients were tested for HIV. When we look, the scale up of ART for diagnosed TB patients, there has been an increase, especially after they start the one-stop service by the end of 2009.

Another country that has actually implemented and rapidly scaled up the one-stop model is Rwanda. In this, the TB clinics actually included a comprehensive ART services in which the TB nurses providing HIV testing and draws blood for CD4 monitoring and also provide antiretroviral and co-trimoxazole therapy. By the end of the TB treatment, patients were referred into ART services for chronic care.

This graph shows, again, the coverage of this model in Rwanda where by the end of 2010, 98-percent of TB patients with HIV were received the co-trimoxazole and 67-percent received ART.

What about the impact of these models on patient cohorts? In the studies that were reported from India and

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examined the referral model where the interventions include training of medical officers and TB and HIV staff and introduction of new referral forms, you can see for those TB patients where almost more than 5,000 for whom their HIV status was not known, only 66-percent of these patients were having HIV testing done.

On the other hand, of all the eligible ART referrals only 56 actually reached the ART center and 27-percent of them received antiretroviral.

This study of the one-stop model from Uganda, which includes is the establishment of a TB/HIV working group in this big hospital, having more than 26,000 HIV positive people under care, and also the development of standardized operating procedures and also establishment of a new one-stop clinic which is separated from the facilities by open space, and also heavily staffed clinic with two medical doctors, three nurses, a peer supporter, and a senior medical officer supervisor.

When we look at the result, the intervention was actually able to shorten the median time for ART initiation from 103 days into 45 days, and the majority of patients received their antiretroviral during the intensive phase, but curiously, the days rate has actually significantly increased after the intervention. However, another study of the same model was in Kenya actually showed a significant improvement of mortality after the one-stop model was introduced.

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We know that HIV/TB and incarceration are intimately linked, and also drug use, so when we really look into any integration into these services, there is a very scanty data and a lack of documented experience. One study from Zambia prisoners reported 23-percent screening for TB and 57 testing for HIV. The All-Ukrainian Network of People Living With HIV with the help of Global Fund has started TB/HIV harm reduction sites, also bringing harm reduction services into the TB clinic. We do not have much impact data on this one.

What are the practical considerations? The first is staff, and space. As you know, the TB/HIV dual epidemic outstripped the services in much of the resource-constrained settings, and this photograph shows a congested OPD in Kenya and the one below in India, and both are the same, with no light, and with no ventilation. Also, these models also involve the renovation and restructuring. In this conference, we actually heard in Kenya dysfunctional toilets were converted into one-stop clinic, and training is also the most important and crucial necessity for [inaudible] nation-wide scale up.

TB infection control is another issue, and we know that people living with HIV are susceptible to TB transmission and this study from Peru shows that 90-percent of all TB transmission in Peru actually comes from two patients with MDR and living with HIV, and [inaudible] report in 2006 showed more than two-thirds of patients were having a hospitalization

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history. Healthcare workers, we know that it is well established have a higher risk for TB transmission and also in the same [inaudible] hospital health workers were having more than five times the risk of being hospitalized for MDR and XDR TB. And, TB infection control can be prevented by opening windows or by introducing mechanical ventilation or germicidal UV radiation. And WHO has the policy to do so.

Another important thing is the documentation in monitoring, unfortunately in many resource limited settings, monitoring and [inaudible] is done by paper waste, and this includes the collecting of data by hand which leads to [inaudible] ART and TB registers and also really taking space that can be used for other services, so we need to digitize the MND system.

What needs to be done? I will summarize what needs to be done into these three areas, and the first: As I said, we know that TB/HIV, drug use, and incarceration are intimately linked, but in what is happening in managing these illnesses or problems in many countries is done in a very vertical and separate management system. Sometimes, even the prison services are not within the Ministry of Health, either with the Ministry of Justice or Correctional Services, or the Ministry of the Interior.

So what needs to be done? We need a greater political leadership and commitment to break up such silos, and minimize

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extreme verticality. We need to ensure joint planning implementation at the minimum, and Ministers of Health should engage into prison health services.

What about TB and HIV programs? In some countries, up to 80-percent of TB patients are HIV infected, and up to 50-percent of people living with HIV are dying of TB, so do we need a separate HIV and TB program in these countries? I think this has to be debated. Sometimes it could be an emotional discussion, but this has to come and find a way, and we have to answer so many questions, which countries and who should swallow who, and also what about the competition and turf protection and the power and balance?

Earlier I said the lack of decentralized ART services is a barrier, but we can use it as an opportunity. As I said, TB services are done by nurses and clinical officers, not doctors in many, many settings, and now we have actually data that ART can also be done by nurses and also health officers, as it is shown in this randomized trial from South Africa, or in this observational study conducted in Ethiopia. We need to use the decentralized TB services to scale up ART and HIV prevention.

Furthermore, there is increased interest for community-based activities, we have to ensure TB and HIV services are integrated into this community initiatives, government should really take leadership in showing that community-based services

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are their priorities; this is an example from Ethiopia where health extension workers who hare community-based workers but paid by the government are really doing a very good integrated work on TB and HIV. This has to be multiplied.

Furthermore, without research, it is always difficult; we need to promote multidisciplinary implementation of research. We do not have quality research, quality data at this point in time, as you have seen from what I presented. We should know what process and impact this integration not only of services but also of the program management will have in bringing this problem to a solution.

We need to look for enablers for successful integration with high impact. We need, also, to involve [inaudible], we need to look for sociopolitical interventions that could trigger and sustain innovation and effectiveness in the health system. What is a problem, what can we take from other services and other programs that really improve the health systems and the management and the integration?

And of course, we need financial support. Research donors should support these studies.

In summary, there is no one model that fits all, and the best model depends on the local contagions and the epidemiology, and we need to seek for increased efficiency among harm reduction services, prison, health, and TB and HIV services, and the effectiveness of these programs has to be

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monitored. As I said, decentralized TB services should be used to scale up HIV treatment and prevention, and we need more funding for research.

I would like to finish my presentation by showing this poster which actually had been put in this clinic in Khayelitsha outside of Cape Town, which was a very pioneer clinic that provides TB/HIV integrative services since 2001. This clinic and this activities expressed is actually being an inspiration to have now the national, practical guidance of TB/HIV integration from South Africa.

If we have political leadership, if we have resources, we can do it.

I would like to acknowledge the following individuals for helping me in preparation of this presentation, thank you very much.

DIANE HAVLER: We need an HIV vaccine, but we also need a TB vaccine, and we do not talk about TB vaccines very much at the HIV meeting, so we are trying to correct that this year, and it is my pleasure to introduce Dr. Tom Evans, who is a Chief Scientific Officer at Aeras who is going to talk to us about TB vaccines, what is on the horizon.

THOMAS EVANS: Thank you very much, it is a privilege to be here speaking on behalf of the TB vaccine community about where we are with TB vaccines. It is extremely dynamic, moving

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very fast and extremely promising, despite the fact that we only really got started about 10 years ago.

One of the important points to make is that we need diagnostics, we need drugs, we need control measures, they will not eliminate TB. Under the best of circumstances using the most appropriate control measures, we can only get to about 1/100th of where we want to be by the year 2050 in terms of the goals of eliminating tuberculosis.

Although in the short run we do need those things to control TB, it is clear that in the long run, we have to develop a TB vaccine; this is data from the WHO from Chris Dye. That data is presented in more detail in the following slide, which I will not go into, the major point on this slide is the best way to establish that is to have a vaccine that can be used both in the latent population as a post-exposure vaccine and mass pre-exposure vaccines in either infants or adolescents. By using those measures, we can eventually go down to the goal of one case per million by the year of 2050.

Where are we at in trying to achieve this kind of goal and the need to actually get a TB vaccine to get to where we want to be, which is to eventually eliminate tuberculosis in the world?

Let us talk first about the challenges, and there are huge challenges in developing a TB vaccine, just like there are huge challenges in developing an HIV vaccine.

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The first is: There is a vaccine at present but it is only used in infants, its duration of effect is somewhere between one to four years, it is unclear exactly how long it works, it prevents dissemination disease, and may prevent pulmonary disease in infants, it clearly does not prevent pulmonary disease in adults and adolescents, and has had zero impact on the transmission of tuberculosis in the world over the last 90 years.

We lack validated animal models, which is a huge issue, and we lack clear correlates of protection of immunity. We lack correlates of protection of immunity not only for vaccines but protection of immunity to understand what the exact protective mechanisms are for those people that get infected but never progress to disease, which is 90-percent of the population. As I am sure you have heard in this conference, about 1/3 of the world's population is presently infected with tuberculosis.

Secondly: Because the incidence of TB is quite low despite the high prevalence, to prove that a TB vaccine works, you need large and very expensive trials. It is almost impossible to do an efficacy trial for tuberculosis right now for less than $20 to 30 million. That is a very large barrier to overcome in order to test and get a proof of concept about whether one of the many approaches which are being used will actually be successful.

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And lastly, and probably most importantly: There is a huge diversity in tuberculosis, there is a diversity in strains, there is a diversity in BCGs, in fact multiple strains of BCG that have very little relationship to each other are used throughout the world, there are different populations as I will go into, and there are clearly environmental factors including nontuberculous mycobacteria that will likely affect people's response to vaccines which may be different in different geographic regions and specifically in different latitudes.

Those are the reasons to be cautious about developing a TB vaccine. Now, why should we be optimistic?

Unlike HIV, we have something that is very important, which is we have natural protection, 80 to 90-percent of people do not get disease when they are infected, and the overwhelming majority of vaccines that have been made and licensed in the world have been made by following the course of natural protection, so we have a huge advantage here over other fields.

We do have a vaccine that partially works, BCG is partially efficacious in children, and we are working hard to try to understand what that mechanism of protection is, although at the moment we do not know specifically what the aspect of BCG induced immunity is that is protecting children from disseminated disease.

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The new TB vaccine candidates protect in animal models, they protect better than BCG, in fact this is a criterion for moving them into the pipeline. However, as I said, because we have not taken new TB vaccines forward into efficacy trials, with the first ones only finishing later this year, we do not know yet how validated these animal models are. But, they do work in the animal models that we do have.

We have clues that will guide immunologic hypotheses, for example we know that low CD4 positive T cells, whether induced by HIV or by other diseases render people more susceptible to mycobacterium tuberculosis infection. We know that people that are treated with anti-TNF inhibitors are highly likely to reactivate, or have a high propensity to reactivate after receiving those inhibitors if they have been latently infected.

And lastly: The new TB vaccines do boost cellular immune responses in multiple clinical studies.

Having said that, the strategies for TB development are not straightforward. This is due to the pathophysiology of the disease. We can either try to get a disease that prevents infection, that is never enters the body as can be seen in the trachea of this patient, so that they never get down and infect the first set stage of disease in the lung, we can try to have a vaccine that also works by taking that person that is

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infected and never goes on to get primary disease early, or does not establish latency.

We can develop disease post-infection to try to prevent people from reactivating their latency, which occurs naturally in 80 to 90-percent of HIV negative people, obviously much higher in HIV positive individuals, and then we can also look to potentially use vaccines as active disease treatment, to shorten the course of disease, especially in MDR and XDR TB, and this is an area that deserves much further study.

Why would we want to conduct TB vaccine studies in HIV positive patients? One thing this audience should realize is that 87-percent of all the TB in the world is not in HIV positive patients. Although TB accounts for one-third of the HIV-related deaths in Africa, remember that the majority of patients with TB around the world do not have HIV.

The incidence, we might want to conduct TB vaccine studies in HIV positive patients due to the morbidity and mortality, and they say this is where we should go first, this is the highest impact population, this is where we should go. It is a population with high mortality, it is a population with a slightly higher incidence, and I will go over that, than the normal population.

There is also the ability to access the medical system if we want to vaccinate young adolescents and adults. It is difficult to get the normal population of adolescents and

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adults who are not accessing the medical system through normal means into a vaccination strategy, and so far we have not been that successful in non-US, non-European countries of introduction of vaccines into adolescents, specifically HPV vaccines, although there is progress being made on that front.

It may be an easier downstream population to vaccinate as you saw the rate of identification of HIV positivity in Africa is going up very highly, so this may be a good population in which to find to vaccinate patients.

There are however many negatives about conducting vaccine trials in this population. First of all: The immune response may be modified, even after the implementation of ART, even with relatively good normalization of CD4 positive T cell counts, we may get a negative result that we then go on to abandon that vaccine which may have worked in a patient that was HIV negative. It is not clear that this is necessarily a population that we can use to bridge back to the HIV negative population which is the overwhelming burden of disease in the world.

The other problem is that even though the WHO has said that INH preventive therapy should be given to HIV positive patients, this is uniformly not applied. Therefore, we have a situation in which the vaccine trials are going to be conducted using one methodology which is not standardly used in many patient populations.

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The other problem from a pathophysiological point of view is it may be that the rate of reinfection as opposed to reactivation may be higher in HIV positive populations, and if we are looking at vaccines that prevent reactivation, and we have a majority of patients that are actually getting re-infected, we may also miss a signal.

Probably most importantly: The is the HIV world and the TB world have a continually changing treatment and prevention landscape, and for a trial that is going to last three to four years, to start a trial with a vaccine in an HIV positive population, it may turn out that the paradigm of preventive therapy, the paradigm of treatment, many paradigms may change during the trial which may make the scientific validity of that trial be less.

Lastly: There are possible issues with the safety of live vaccines given to HIV positive patients.

What is the reality of conducting TB vaccine trials in HIV positives? There was a lot of momentum for doing these trials approximately six to seven years ago, and the reason was is people said look, if you go into the general population, you will get an incidence of maybe 0.5-percent or 0.6-percent, but if you go into the HIV population we have incidence rates of 4, 5, 6, 7, 8-percent, and therefore, you can use one tenth the number of patients to find out if your vaccine works, and

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instead of doing a $20 million trial, you can do a $4 million trial.

Unfortunately this is not absolutely true. First of all: The increase incidence as you saw in the figure presented earlier is made up almost entirely of those that are skin test positive, which means that we probably need a vaccine that is designed to prevent reactivation, although that is not entirely true.

This is seen on the right side of the graph where the same data that you saw before is broken up by the skin test positivity shown to you. That means that the population down at the bottom which is the population which is skin test negative has an incidence rate over three years that is approximately 2-percent.

In Botswana, that incidence rate in 2-percent is not highly different from the standard background population. In fact, if you look at the incidence rates of people that are on ARTs, have a CD4 count greater than 200 and are given preventive therapy, they are in general not, over a short period of time, over a two to three year period that you would do your vaccine trials, are not highly different than the general population.

This brings us back to the question: As a TB vaccine developer, should we do our trials first in this high-risk population that has a slightly higher incidence, or should we

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do our trials in the general population and then bridge back to HIV?

Now a very important point: In 2000, the clinical vaccine pipeline had one candidate in it, and you could fit the number of researchers in a minivan, and this is where we are today, so very importantly we now have one candidate in a phase III trial in India, three candidates in phase IIb trials, four candidates in phase II, and four in phase I, these are all in human trials. Importantly, more importantly, I think, is that we are using a diversity of approaches, both recombinant BCG, protein adjuvants, viral vectored vaccines, and eventually nucleic acids.

Up in the phase IIb trial you will see that there is an MVA85A trial, that is a very important study that is ongoing in HIV negative infants at the moment, it has enrolled 2,800 patients in Cape Town, South Africa, and we will be unblinding that trial at the end of this year with results to be presented next year, the first large efficacy trial of a new TB vaccine conducted in quite a while.

These four candidates are in trials in HIV positive patients, and I need to tell you that all candidates will go through HIV positive patients in terms of assessing their safety risk.

A few specific candidates I would like to address, the first is M. vaccae, I will not go through any detail but there

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was a trial done in Tanzania by a group led by Ford von Ryan out of Dartmouth, in which they did a phase III randomized controlled trial in Tanzania. This was five doses of a heat-killed M. vaccae vaccine which is a nontuberculous mycobacteria and they saw protection in a secondary endpoint of definite TB, although they missed their primary endpoint of disseminated TB, and there was no effect in those cases that were probable TB. The vaccine was safe, and there was very low lost to followup of 18-percent over the time of the trial, which was three years.

MVA85A is a modified vaccinia Ankara vaccine that is being studied in a large number of population, it induces CD4 positive T cell responses, those CD4 positive T cell responses are less robust in HIV uninfected individuals as is shown in the graph here, but they do persist, and they can be boosted by the use of a second vaccine up to a level that is consistent with other vaccines.

A phase II randomized double-blind placebo-controlled trial is ongoing in HIV positive infected adults in South Africa and India supported by EDCTP, over 400 subjects have been enrolled to-date, but it will be quite a while before we have the results of that trial.

There is an Ad35 vaccine that has entered into a phase IIb trial also in infants with support of NIH, and a variety of other funders, and that vaccine has also gone into HIV-infected

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BCG-vaccinated patients at the Aurum Institute in South Africa, was shown to be safe, and like the MVA, there was no change in viral load or CD4 counts in one year of followup after vaccination.

The VPM1002 vaccine is a live mycobacteria vaccine that expresses listeriolysin, it was shown to be safe in a SCID mouse model, and it is presently being studied in HIV uninfected infants in South Africa, and is slated to enter next year into a trial in HIV exposed newborns to get around the problem that BCG is not recommended by WHO for infants in South Africa. This recommendation is essentially never followed in clinical practice.

Importantly: What is on the horizon, what has happened in TB vaccines? Since 2005 you have heard there has been about $600 million invested into tuberculosis research, and we are now beginning to see the fruits of this, we are beginning to have some of the scientific understanding of the way to move forward with tuberculosis vaccines.

There is a rich pipeline, and 15 new vaccine clinic candidates have entered clinical trials. We have a very robust and diverse pipeline of candidates, which are very important for testing new hypotheses. We have promising activities looking at new biomarkers, mostly based on gene expression signatures and systems biology.

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We have capacity for vaccine production and we have shown that we can carry out large-scale efficacy trials in infants and are starting a study soon in adolescents next year in multiple continents.

We have a better understanding of safety and immunogenicity, and in the decade to come, in starting next year we will have the first efficacy data for proof of concept trials which are underway, we intend to have a better understanding of the correlates of immunity which will massively accelerate the testing of future vaccines, we will start multiple phase III studies in the next decade, and there is the possibility of a TB vaccine licensure, but even if we do not have the licensure, we will have the knowledge and the scientific basis to move forward. Thank you.

MARK HARRINGTON: Thank you so much Dr. Evans. So we have heard from our speakers today about the scientific promise that lies before us about the possibility of ending TB in our lifetimes, but we are not going to get there without solidarity, commitment, and political will, and so I am absolutely thrilled to be able to introduce a special commentary on pediatric HIV and TB by Oscar, Emmy, Tony, and Grammy award-winner Whoopi Goldberg.

WHOOPI GOLDBERG: I assume before I start reading my prepared statement that you all are aware of all of this that they have been talking about, is that so? Is this all

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information you know? Yes? Okay. Because I did not know it, a lot of it I did not know, and so for me, it is a little shocking to hear folks say we need to raise more money, we need to get more help, we need to get all of these things, and I always thought we were so much further ahead than it turns out that we are. I am really thrilled to be here to do whatever I can do.

I have been talking about folks living with HIV for years, from before we even knew what AIDS was, and I have always been concerned for the children affected, and I one day believe that I will wake up and there will be days when no child dies from an HIV-related cause.

As I said, some of this information that I have gotten is shocking to me. Who knew that TB was something that we had to be concerned with? Now, I say that as an American, because for us, TB has been gone for a long time, so we do not listen to the conversation when someone introduces the fact that HIV is now in partnership with TB, we do not deal with it.

But, we are going to start to, it is going to come back and bite us in the butt, because we are in a situation where parents are not immunizing their children and so we are going to start seeing a lot more of these kinds of diseases rear their ugly heads and so I figure as an American standing here talking to you all, some of you are American, some of you are

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not, we are going to have to come to terms with this and join in making this partnership dissolve.

Because we, as Americans, are going to be the ones left in the dark not recognizing that HIV and TB are something we have to be dealing with now rather than later. That is just my opinion.

The issue of tuberculosis, about 9 million people become ill with TB, 1.4 million people die of this disease, almost 4,000 deaths every day, 200 of those children, and half a million of them are women. Half a million. Why do women always end up with the fuzzy end of the lollipop?

We have got to take care of the kids, we have got to clean the house, we have got to clean the place, we have got to make sure everything's okay, we have got to be the nurse to everybody, and then for some odd reason we are the ones that are dropping like flies, and we are the ones that have to beg for help all the time.

It is just a drag, TB is an opportunistic disease, it takes advantage of weak or compromised immune systems and it is the most common illness and the leading cause of death in people living with HIV. As a result, TB is responsible for killing 1,000 people living with HIV every day.

And, it is preventable. We can prevent it; we can probably come close to curing it-ish. But the thing that knocks me out more than anything is that very young children

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are at a special risk of having more severe, often fatal forms of this disease such as TB meningitis which can leave children blind and deaf, paralyzed, and mentally disabled.

The truth is, TB is being neglected in children, even though it causes unnecessary suffering and death, the world over, especially in communities affected by HIV. All told, at least half a million children have become ill with TB ever year, today we have high hopes of zero transmission of HIV from mother to child.

But I do not think that is going to happen unless we address TB as well, because if you add the fact that pregnant women living with HIV are ten times more likely, and their babies are more likely, they are at more increased risk of developing TB. Clearly, you can see the devastating link between TB and HIV. There is no way to get around it, it is linked, they are in partnership like a Hollywood couple.

In 2009 there were about 10 million children in the world who had been orphaned by the death of a parent because of TB. It is really typically a family problem, the vast majority of children who become ill with TB catch it from a close family member, before their TB has been diagnosed or the treatment has begun, so when you realize that, you see it is easy enough for us to recognize that you cannot protect children against TB without addressing it from within the family and the wider community.

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The good news is that TB, as I said, is preventable. In a vast majority of cases, it is curable, even in people living with HIV. While much more still needs to be done to improve our options for vaccines and drugs and diagnostics, we already have in our hands some effective tools that can help us weather the storm of this epidemic, however the tools are currently not being used in countries that need them the most due to persistent funding gaps for TB. No more missed opportunities while so many people are dying.

How do you know what is killing people, see it, know that you can do something and let it happen anyway, and then cry about the fact that it is happening? You cannot have it both ways.

Either you get up off your butt and you get out there and you start saying we know what we need to do, and if these people die, it is on you, it is your fault, because there is something we could have done. That is just my opinion; do not hold anybody accountable for what I am saying. That is just what I feel.

This is ridiculous to me; if you see the problem, fix it. This seems to be a worldwide issue; people see the problem and go to dinner. People see the problem, they buy some new shoes. People see the problem and they stigmatize the people. I say we should stigmatize everybody, blondes should be

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stigmatized, brunettes, it should be a stigma to be a brunette. It should be a stigma to have a big butt.

It should be a stigma to have a wide nose. If we stigmatize everything, nothing is a stigma, then we can get past all this BS that people lay out and say oh, this means this to me. It should mean nothing except that you need some help, and people will not take help because they say that someone will know. Well, the shocking part is people know anyway. So why not just get the help?

We need to make sure that existing interventions that we know work are being implemented in the countries where the burden of TB and HIV is high and they can reach the people who are in need. Yes there are challenges in preventing, diagnosing and treating TB, especially in children, but that should not stop us from making sure that every child at risk of TB is found and has access to the best care.

We can do a lot, we can focus our efforts on finding vulnerable children but also their moms, and pregnant women at risk of TB and screen them with a simple questionnaire and put them on preventative therapy to stop them from becoming sick or after diagnosing them with TB, stop them from passing it on, we can save lives. Since TB is a family problem, every time someone becomes sick with it, all the children in the household of the person living with TB have to be examined.

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Since pregnant women and mothers and children living with HIV attend maternal and child health services, family planning, prenatal care, prevention, all those things, we have to screen them for TB at every health visit, but also all pregnant women, mothers and children with TB should receive HIV testing and counseling to maximize their chance of survival, to ensure that they get life-saving antiretroviral therapy to help.

To national policymakers, health program managers and international agencies working on material and health care needs, needs to pay closer attention to TB and countries most affected, diagnosis and treatment, activities that are part of what needs to happen, by following these simple steps, millions, millions of lives can be saved.

But you can achieve even more, because imagine the impossible end, hold up. This is how you know you are getting old. You think you know what you are reading, and then something totally different appears on the paper. And yes I have it written down because you know I cannot remember it.

Okay, I am back. By following these simple steps, millions of lives could be saved, but we could achieve even more, even imagine the impossible end of the unnecessary suffering of children from TB with more research and new, better, simpler, child-friendly tools.

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Some progress has been made but not nearly enough and not fast enough, once again due to persistent funding gaps. The only available TB medicine today, BCG, was first used in 1921, when I was born, I look good, huh?

You know in America they say Black does not crack and it is true. But it neither offers protection to all children nor does it necessarily last throughout childhood. The BCG prevents many severe forms of TB in very young children including TB meningitis, but it cannot be used for infants. That is not good; we need something we can use on all children, on everybody, that is what we have to do.

We don't have a simple rapid diagnostic tool that can be administered in any setting, the clinic, the home, the laboratory, there is a desperate need for an easy test like a mouth swab, something you just put it in the baby's mouth, you could even put mint on it, babies love mint, I do not know why but they do.

But that would be nice, something simple, my God, we can find an ant taking a little poop under a staircase from space, we should be able to develop something this easy, we can talk to people in other countries endlessly and yet we are having a hard time finding a way to save people's lives. I find it extraordinary, but maybe that is just me.

In conclusion, TB treatment and preventative therapy for children lasts at least six months, and the regimens have

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side effects, child-friendly drug formulas do not exist yet, which means the children in need could receive incomplete treatment.

This can lead to death, or development of resistant strains of TB that are much more difficult or impossible to treat. It is really time for the special needs of children, as well as pregnant and nursing women, whether HIV positive or negative, are considered in the development of new drugs and new drug regimens.

The theme of AIDS 2012 is Turning the Tide Together. I would like to see that happen, I really hope that everybody attending the conference will recognize that to end AIDS we have to join together to tackle TB and HIV as one disease. We have to do it now, because children do not wait, they keep coming and we have a responsibility.

Now listen, you guys sat and I think you for sitting through this with me. I know you will do what you can, I know everybody in here knows what needs to be done, and you are doing your best. We will just keep trying harder to get the word out, we will get the word out to the people who have the money, and remind them that this, too, is part of this legacy.

I want to say how thrilled I am to be here, how happy I am to see the quilt once again, because I have not seen it in a very long time. I thank you all for hanging, I am done.

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DIANE HAVLER: Thank you very much, that was absolutely a splendid close to this session. I would like to thank all of you in the audience and all of our speakers. This session is now closed.

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