Plenary: HIV in the Larger Global Health Context
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JEAN-FRANÇOIS DELFRAISSY: Jean-François Delfraissy director of the French National Agency for Research for AIDS and Hepatitis. As the IAS $2,000, IAS and ARNS young investigator awards are jointly funded by the IAS and the ANRS to support young researcher with the most innovation [break in audio] originally [break in audio] for presentation must be under 35 years of age. One prize is awarded each of the five conference tracks along with a special HIV cure prize this year. And the winners this year are —

The first winner is Rik Schrijvers from Belgium for the outstanding track A, abstract, Dissecting HIV-1 integration site selection using a human LEDGF/p75 knockout [applause].

MALE SPEAKER: The second one is Vikrant Sahasrabuddhe, for the abstract HPV genotype attribution of anal neoplasia in HIV-positive MSM: estimating the preventable fraction and disease misclassification. Congratulations [applause].

The third one is Renee Heffron from the U.S. for Association of injectable contraception and risk of HIV-1 acquisition in women in HIV-1 serodiscordant partnerships: persistence of effect in multiple sensitivity analyses [applause].

Kathleen Deering, from Canada for Mapping spatial barriers and facilitators to HIV testing by work environments among sex workers in Vancouver, Canada [applause].

Caitlin A Matson from U.S. for Integration of infant HIV testing at nine month immunization visit in South Africa: a proposed model of service delivery [applause].

And finally there's a special HIV cure prize is awarded to Nitasha Kumar from Australia for the outstanding abstract Myeloid dendritic cells and HIV latency in resting T cells [applause].

JEAN-FRANÇOIS DELFRAISSY: The next award is for IAS and Coalition for children affected by AIDS. A prize for excellence in research related to the needs of children who are affected by AIDS. I'm please to invite on stage, Ameck Ayong, Member of the Coalition of Children Affected by AIDS; and Senior Manager for advocacy Nelson Mandela Children's Fund to present with me the is Coalition for Children Affected by AIDS prize for excellence and research related to the needs of children affected by AIDS.

AMECK AYONG: Good morning. The $2,000 prize is jointly offered by the International AIDS Society and the Coalition for Children Affected by AIDS. To underline our efforts to make children have priority in the international response to HIV. The price is awarded to an investigator whose abstract demonstrates excellence in research, that is likely to lead the advances in the understanding of needs of children, and improve services for children affected by HIV and AIDS.

The 2012 IAS Coalition for Children Affected by AIDS prize for excellence in research related to the needs of children affected by AIDS, has been awarded to Professor Gabriel Anabwani in the condition of his outstanding abstracts. The psychosocial impacts of HIV on the siblings of affected children [applause].

JEAN-FRANÇOIS DELFRAISSY: A final award for this morning is a presentation for TB/HIV research prize. IAS TB/HIV research prize presented. TB remains a leading cause of morbidity and mortality among people living with HIV. And the HIV's the strongest risk factor for the movement of Tuberculosis and one-third of people living with HIV are co-infected with TB.

The IAS TB/HIV research prize is an incentive for researchers to investigate pertinent research questions that affect TB/HIV co-infection, and the operational effectiveness of co-TB/HIV collaborative services. The 2,000 U.S. dollars prize is offered by the International AIDS Society to generate interest and stimulate research, and the best clinical and operational research, and TB research core care and treatment.

This prize on this occasion is awarded to Jonathan Golub from the United States for the outstanding abstract the TB/HIV in Rio de Janeiro study: a step-wedged cluster randomized trial measuring the impact of tuberculosis (TB) screening and isoniazid preventive therapy (IPT) on

incidence [applause]. Thank you.

FEMALE SPEAKER: Please welcome Dr. Teguest Guerma, Director General of the African Medical Research Foundation [applause].

TEGUEST GUERMA: Ladies and gentlemen, good morning. HIV is the main cause of failure in meeting the target of tuberculosis control. TB is the leading cause of death among people living with HIV/AIDS. To end AIDS the management of TB/HIV co-infection according to the new governmental guideline should be an integral part of our strategy. This morning I am very pleased to introduce one part who has made great contribution to HIV/TB and who has worked for more than 20 years in Africa, Dr. Anthony Harries.

Dr. Harries is currently a Senior Advisor at the International Union Against Tuberculosis and Lung Diseases in Paris, an Honorary Professor at the London School of Hygiene and Tropical medicine. He's a physician and a registered specialist in infectious disease and tropical medicine. His main interests are in the field of tuberculosis, HIV/AIDS, tropical medicine, and operational research.

Dr. Harries has started work in 1983 in Northeast Nigeria. And he moved in 1986 to Malawi, where he was consecutively consultant physician, foundation professor of medicine at the new medical school in [inaudible], National Advisory to the Malawi Tuberculosis Control program, and

National Advisor in HIV/AIDS Care in Blantyre, and the Minister of Health responsible for scaling up antiretroviral therapy in the country.

Dr. Harries has received several awards and prices for his work, and in 2002 was appointed officer of the Order of the British Empire for services to work in tuberculosis in Africa. Please join me in welcoming Dr. Tony Harries [applause].

ANTHONY HARRIES: Teguest, thank you very much in deed. Ladies and gentlemen, good morning. I'd like to thank the conference organizers very much indeed for asking me to deliver this lecture. It's a great honor, it's a great privilege, and one I share fully with my friends and colleagues. I would like to take the liberty of expanding the title of my talk and focus on basically turning the tide and also reducing deaths.

The reason it's showing here, in 2010 of the 1.1 million people globally with HIV associated tuberculosis, 350,000 died. Given that tuberculosis is curable and HIV/AIDS can be treated, all be it with lifelong therapy, one has to ask these high death rates occurred, three reasons.

In people living with HIV/AIDS tuberculosis was not diagnosed and not treated. In patients with tuberculosis HIV was not diagnosed, and thus co-infected TB patients were not referred to HIV care and treatment. And when the two diseases were diagnosed and treated this often happened far too late. These failures must be rectified, and I believe that the

application of new science and the strategic use of new diagnostic tools make this possible.

HIV/TB is a global problem with focal areas in South Asia, Eastern Europe, Latin American, but the epicenter is Sub-Saharan Africa. This region houses 82-percent of the global burden of HIV/TB, and suffers 71-percent of its deaths. The scale ups of antiretroviral treatment ART has been a remarkable and deservedly applauded success, but not all patients do well. For example in Africa, between 8-percent and 26-percent of patients starting ART die in the first year of therapy, and both diagnosis and undiagnosed TB are major causes of this mortality.

The evidence of that statement comes from autopsy studies, many conducted in the pre-ART era, some more recently in the ART era, showing the deadly role of tuberculosis, often disseminated, often unrecognized life. Similarly in the pre-ART era there were high case fatality rates in HIV infected TB patients, during the course of TB treatment. These death rates occurring early on in the course of treatment, and increasing as the CD4 count decreased. Thus we need early interventions against both HIV and TB if we are to avoid these deaths.

In March this year WHO launched its updated policy on TB/HIV collaborative activities to reduce the burden of dual disease. This is a great document. It borrows from the framework of a 2004 interim policy, and consolidates evidence

over the last eight years from clinical trials, observational studies, and best practices. This policy allows us to articulate four important spheres of work shown here, which if implemented will reduce the burden of HIV/TB and will reduce death.

First we can prevent tuberculosis in people living with HIV/AIDS by early antiretroviral treatment and isoniazid preventive therapy, IPT. There is now compelling evidence that ART is a powerful TB prevention tool. A systematic review and meta-analysis of 11 studies from around the world show that ART overall significantly reduces the risk of tuberculosis by 65-percent compared with no ART, with the results more apparent in those with a lower CD4 count.

At the program level studies in Brazil, South Africa, and Malawi show that as ART coverage reaches a high proportion of eligible patients in the community, TB case notification rates in that community decline, and in Malawi that decline was noted for both new tuberculosis and recurrent tuberculosis.

The challenge that we currently have, particularly in Africa is that the majority of people with HIV/AIDS who start ART do so at low CD4 counts of between 100 and 150, in contrast the majority of HIV infected TB patients are diagnosed at higher CD4 counts of between 150 and 200, and thus HIV diagnosis and start of ART are too late to prevent tuberculosis, and the TB prevention role of ART is largely

squandered. We must start ART earlier and we start ART at higher CD4 counts.

Randomized control clinical trials now provide definitive evidence of the TB protection role of ART at these higher CD4 counts. For example in Haiti, in patients starting ART at a CD4 count of between 200 and 350, there was a 50-perecent reduction in TB incidence compared with those starting ART and lower CD4 counts. This benefit was matched by a reduction in mortality. In the Seminole HPTN 052 study the early ART group started therapy at a CD4 count of between 350 and 500.

In this early group not only there was a 96-percent reduction in HIV transmission, which long term and at the community level will reduce HIV/TB, but there was also a 40-percent reduction in serious HIV related clinical events driven mainly by extra pulmonary tuberculosis.

Mathematical models also predict the huge TB prevention benefit from early ART. These models using data from nine African countries show that a strategy of universal and annual HIV testing, combined with immediate start of ART for those HIV positive, for so called test and treat approach, would result in a 48-percent reduction in TB incidence in five years, and 98-percent reduction in 40 years, and over that 40 year period we could avert six million TB cases.

A tough and urgent priority then is to assess a efficacy, feasibility, safety, costs, social and population uptake of the test and treat approach, and I'm pleased to say that the global research community is already responding to this challenge. This map showing the countries and the sites where such research is either about to start or has already started. Some countries are also considering this as a national strategy, for example in Malawi test and treat has been used now for over one year in pregnant women, and we have lessons to learn from these bold national approaches.

Life however is never simple and there is a caveat. In the high HIV/TB burden areas of Southern Africa ART alone is not enough. In this eight year follow up study, although time spent on ART and time spent at high CD4 count strata, both reduced the risk of tuberculosis, that risk never came down to the levels seen in non-HIV infected persons. Other TB prevention interventions are needed.

Here we come to isoniazid preventive therapy, IPT. Given daily for six months this reduces overall the TB risk by 33-percent, with the protective affect mainly seen in those with a positive tuberculosis skin test in who risk reduction is 64-percent. Based on this evidence WHO guidelines from 1998 to 2009 emphasized that IPT be given to people living with HIV who had a positive tuberculin skin test. Unfortunately scale up has been extremely poor. The two major challenges being the

process and the assessment of tuberculin skin testing, and reliable exclusion of active TB.

To overcome this inertia, WHO last year released updated guidelines, in which it explicitly states that tuberculin skin testing is not a requirement for starting IPT, although it can be used when feasible? This has had the desired effect, implementation is improving, and by the end of 2010, 25-percent of people living with HIV in care and eligible for IPT received TB prevention treatment.

IPT is currently recommended for six months; new data however from Botswana forced us to reconsider this advice even though this will have implications for IPT delivery. In Botswana and on the left graph, 36 months of IPT reduced the risk of tuberculosis by 40-percent compared with six months of IPT, but on the right graph, when IPT was stopped, TB incidence rapidly increased to that or a control arm, suggesting that in these high TB exposure environments, continuous IPT is necessary to maintain a TB prevention effect.

Finally observational studies in Brazil, South Africa, and also Botswana show that IPT in addition to antiretroviral therapy results in a synergistic decline in risk of active tuberculosis. There are two randomized controlled trials, Temprano in Cote d'ivoire, and HAART IPT in South Africa that are addressing this issue, and we eagerly await their results.

While we wait, though, an implementable strategy exists. In people living with HIV we start ART as early as we can. When people are stable and asymptomatic we add in IPT, and we continue on this indefinitely providing there is no toxicity and providing there are no side effects.

A word about children. Although TB is not the great killer in children that it is in adults it is never the less an important cause of their death. ART is recommended in children under the age of two years with confirmed HIV infection regardless of CD4 count, and in trial conditions this reduces mortality and reduces risk of TB. However despite ART that risk of TB remains high, and unlike the situations in adults, the addition of IPT does not bring that risk down. The conundrum of how best we prevent tuberculosis in young children is not resolved and requires further science.

If we don't prevent tuberculosis we then need to move to the second sphere of work, to find, diagnosis, and treat TB in people living with HIV. So called intensified case finding, which is packaged together with IPT and infection control under the name of the three "I's". We now have a simple and standardized TB symptom screening tool, which has been validated in clinical studies and also in the field.

A negative screen effectively excludes tuberculosis and moves a person in the direction of IPT, a positive screen indicates the need for further TB investigation. The usual way

of investigating for tuberculosis is through sputum smear microscopy, followed by chest radiography in those in whom the sputum smears are negative. While this has been the main stay of TB diagnosis for years, it is time consuming, it is costly for the patient, and it is diagnostically insensitive, particularly at low CD4 counts. TB culture takes too long and costs too much. We urgently need better, quicker, cheaper diagnostic tests for tuberculosis [applause].

In this regard an important and revolutionary development is a sensitive and specific commercially available, automated test, nucleic acid amplification test, Xpert MTB/RIF, which can be used with sputum smears and other specimens in both adults and children. Minimum laboratory expertise is required to run this machine and this assay, and the result is produced in under two hours.

TB yes or no, rephanthisan [misspelled?] resistance yes or no. WHO recommends that we use this as the initial diagnostic test in patients with suspected HIV associated tuberculosis, but the challenge that confronts us all, is far how peripherally can we decentralize this test to bring it as close to the patient as possible, and how far can we reduce the quite high costs.

Enough of promising alternative, particularly in patients with advanced immune deficiency. This measurement of urine lipoarabinomannan, urine LAM, a cell wall component of

lyco bacterium tuberculosis. This can now be easily measured with a TB LAM determined test strip, the later cost is $3.50 per strip, and producing a result in 30 minutes.

This offers real point of care potential for diagnosing TB. It is very specific and sensitivity increases as the CD4 count declines, reaching 66-percent at CD4 counts of below 100. Diagnosis is not just about accuracy, it's about feasibility, it's about speed, it's about cost, and it's about impact in saving lives, and this has been and continues to be the Achilles heel of the three "I" strategy.

A way forward then at all levels of the health system is to use a combination of different tests. Sputum smears to pick out those with the most infectious TB. Urine LAM to identify those with the most advanced immune deficiency, chest x-ray when available. We must work hard to develop the point of care potential of expert MTB/RIF.

Given the problems with diagnosis it is not unreasonable to consider the option of empirical anti-tuberculosis treatment in patients with severe advanced immune deficiency. The rationale is that as the CD4 count declines the risk of tuberculosis exponentially increases, and at a certain point we have more to gain than lose by treating empirically for TB.

Empiric TB treatment, treats all of those with active tuberculosis and it prevents tuberculosis in those who do not

have TB. Two trials are currently underway to assess safety and the efficacy of this approach.

This brings me to the third sphere of work. If TB is the entry point to care it is essential that we diagnosis and treat HIV. The key interventions are provider initiated HIV testing and counseling, cotrimoxazole preventive therapy which in its own right reduces mortality by up to 46-percent, and ART which in its own right reduces its own right reduces mortality by up to 95-percent.

These two interventions together having an additive and a synergistic effect. In the last 10 years there's been a gradual increase in the proportionate TB patients tested for HIV, reaching 34-percent in 2010, with some regions doing better than others. Studies in West, Central, and East Africa highlight the importance of moving HIV testing upstream to include patients with suspected tuberculosis in who the sputum spears are negative.

In Zimbabwe, 63-percent of such patients were HIV positive, most with a low CD4 count. During a 12-month follow up 18-percent developed active tuberculosis, 12-percent died, and only 15-percent were placed on ART. These poor outcomes could have been avoided if the HIV infected patients had been placed much earlier on antiretroviral treatment. ART is the key intervention here.

The WHO 2010 guidelines highlighting that all HIV positive TB patients are eligible for ART regardless of the CD4 count, and that ART is initiated as soon as possible after the start of TB treatment. The question of when best to start ART has been clarified by three superb randomized control clinical trials published last year.

CAMILIA, SAFID [misspelled?] and STRIDE and the key message from these three trials plus other more recent studies is that if we start ART within two to four weeks of start of TB treatment, this reduces death, particularly in those with low CD4 counts. In this group, IRIS, immune reconstitution inflammatory syndrome, is more frequent, but this complication is outweighed by improved survival.

Two quick points: in HIV infected patient with TB meningitis however, we should consider delaying ART because IRIS within the confined space of the central nervous is a dangerous complication. In patients on second line ART taking protease inhibitors, we cannot use rephanthisan because of drug/drug interactions, but referbutin [misspelled?] is a safe and effective alternative.

What we need to do with this drug is reduce the cost, is work out optimum dosing schedules and fairly urgently introduce this drug into a fixed dose combination pill with other TB medications so that it is available for patients in the field at the program level.

HIV and drug resistant tuberculosis is lethal and as these data from Tugela Ferry show, in the absence of prompt diagnosis and prompt HIV intervention, there's extremely high mortality. Observational studies show that both ART and CPT reduce this mortality and in the absence of any randomized controlled trials in this area, we follow the same advice as the drug sensitive tuberculosis about when to start HIV interventions.

This brings me to the final sphere of work: delivering services in health facilities at the community level. In health facilities, it is so important to co-located TB and HIV clinics in the same facility under the same roof so the patients do not have to walk miles from one service to another. For example, in South Africa when the clinics were in separate geographical locations, only 11-percent of co-infected patients with a CD4 count below 50 started ART before weeks of TB diagnosis and failure to co-locate is probably responsible for why only 46-percent of HIV TB patients globally accessed ART in 2010.

Better still, we could integrate the services in the same clinic. A way forward here is to offer a comprehensive package of HIV/TB services for the co-infected patient during the duration of TB treatment and when that is finished, we move the patient to HIV services. This should not be difficult to do, but if we do it, we must insure the practice of good

infection control standards so in this environment tuberculosis is not passed from one person to another.

Finally we must get out of the health facility and into the community and engage in community interventions around prevention, diagnosis and treatment of HIV and TB. For example, in Blantyre, Malawi, HIV self-testing using oral saliva tests was extremely popular in men and women and this is a way of testing HIV testing uptake at the community level.

I cannot in the time allotted me do justice to these three excellent community studies looking at case finding and TB prevention at the community level, detect TBs with AMSTAR in Tegela. The key positive messages I take from these studies are that active TB case finding using mobile vans, household visits using a package of HIV TB services to contact of TB patients enable us to identify TB much earlier in the community and enable us to reduce TB transmission and reduce TB prevalence at the community level. What we need to do here is move research in policy and practice.

Finally, we need to work out how we can incorporate active case finding and TB prevention into these increasingly popular community multi-disease campaigns, such as this one in Kenya Larambi which focused on HIV, malaria and diarrhea. There is plenty of spoken here for innovation and implementation.

In conclusion, the WHO TB statement this year emphasized zero TB deaths and I think this fits very well with the bold vision articulated with UNAIDS, WHO and others of the three zeros: zero new infections, zero discrimination, zero AIDS-related deaths.

For these slogans to count, to mean something, to have teeth, we have to do three things. We must continue doing the science to plug the gaps in our knowledge, we must implement what we know works and be held accountable and finally we must use the full weight of our collective conscience to tackle the poverty that is at the root of this HIV/TB epidemic. [Applause].

Any premature death due to HIV/TB is a tragedy and I leave you to read you this short passage from the poem, No Man Is An Island, written by one of England's 16th century poets, John Donne, and while you do that, I'd like to draw your attention to the fact that there's a paper published today on this plenary in the journal of the International AIDS Society if you want to read more about HIV/TB. I'd like to thank everybody listed on this slide for their great help and support with this presentation and I'd like to thank you very much for your attention. [Applause].

I haven't quite finished. One minute, Marie wants to come up and say a few words to you.

MARIE: Good morning. My name Marie. I'm from an organization called Results Australia. What a great week we've had in this beautiful city and what amazing progress we've made. The last time the AIDS conference was held here in the U.S. more than 20 years ago, no one would have dared to talk about an AIDs-free generation, yet because of your work, here we stand on the cusp of the end of AIDS.

Now I want you to do something for me. If you were handed a white t-shirt on your way into this room, would you please stand up right now? Please stand up if you have a white t-shirt. I want you all to look around the room. If this room was full of people living with HIV, those standing would be dying of TB. TB is responsible for 1 in 4 HIV-related deaths, making it the leading killer of people with HIV. Nelson Mandela said, "We cannot win the battle against AIDS if we do not also fight TB."

We need to have made more progress on this by the next time we meet in Melbourne, in my country, in two years time. [Applause]. We must all work together to create the political will to once and for all put an end to the devastating effects of TB and HIV. I invite you to join me in this work at www.action.org to raise your voice and take action. Let's move past 1 in 4 deaths from TB and celebrate the next time we meet again in Melbourne. Thank you. [Applause].

FEMALE SPEAKER: Please welcome Dr. Carl Dieffenbach, the direction of the division of AIDS at the National Institute of Allergy and Infectious Diseases. [Applause].

CARL DIEFFENBACH: Good morning everyone. Judith Currier is professor of medicine and chief of the Division of Infectious Diseases and co-director of the Center for AIDS Research and Education Center or CARE in the department of medicine at UCLA. She also holds the important role as vice chair of the NIH sponsored AIDS clinical trials group and is the principle investigator of the UCLA AIDS Prevention Treatment and Clinical Trials Unit. The unit has four sites in the city of Los Angeles, is involved in community-based HIV prevention, vaccine research and therapeutic clinical trials.

Her research is focused on the understanding the factors that contribute to the long-term complication of treated HIV disease and study of HIV treatment as well.

Judith has been at the forefront of efforts to understand the role of gender in treatment outcomes and enhanced research on women with HIV, specifically maternal health outcomes following interventions to introduce mother to child transmission.

The title of Dr. Currier's presentation today is the Intersection of Non-Communicable Disease and Aging in HIV Infection. Please join me in a round of applause to welcome Dr. Currier. [Applause].

JUDITH CURRIER: Well, thank you very much, Carl and thank you all for coming this morning. I want to thank the organizers for inviting me to give this talk, but also for making aging and HIV such a prominent theme at this year's conference. Here we are in 2012, planning to treat millions of people with HIV for decades to come and we better figure out how to do it right.

Do not regret growing older. It's a privilege denied to many and we now have the privilege to face this challenge of providing HIV treatment for people over a long lifespan.

Access to antiretroviral therapy has extended the lives to millions worldwide. Improvement and longevity appears greatest for those who start ART earlier and prior to development of AIDS. Life expectancy for treated HIV is approaching that of the general population, however in many studies, there appears a persistent ten year gap.

This slide demonstrates survival projections from the age of 25 over different periods of time. You can see as we've moved from the pre-ART era in 1995 to early ART and later ART era for survival is extending, but not quite backed to the normal population.

Now more recent data from the cohere cohort in Europe examined mortality rates of patients on ART compared to the general population and they focused on people who achieved a CD4 count above 500. Among the non-injection drug users with

high CD4 counts on ART, they found that survival was similar to the general population and the longer the duration of CD4 remained above 500, the better.

Importantly, even among this group, a prior diagnosis of AIDs was still associated with higher mortality.

So it should be no surprise as treatment has improved, survival has improved, the population of people living with HIV is aging and in the U.S. back in 2007, the median age of people living with HIV was 40 to 44. This has been increasing in 2008 30-percent of people living with HIV in the U.S. were over the age of 50. It's estimated that at this rate, by the year 2020, half of all people living with HIV in the U.S. will be over the age of 50.

Now adding to this is the fact that 11-percent of new infections in the U.S. occur in people who are over the age of 50 reminding us that age is not a condom.

Aging with HIV is occurring around the globe. These data from a rural district in KwaZulu-Natal in South Africa predict the proportion of the population that will be over the age of 50 over the next 30 years and that you can see in the blue bars both in men and in women, this number is increasing.

Nathan Ford from MSF shared with me that in their cohort of 18,000 on ART in Africa, 12-percent are currently over the age of 50 and as people age, their risk increases for non-communicable diseases. What are these diseases?

These are infections that are non-infectious and non-transmissible between people and they include cardiovascular disease, cancer, diabetes, chronic respiratory disease. These are the big four with common risk factors, but in addition includes renal disease, neurologic diseases, mental health disorders and gastrointestinal disease. NCDs are a huge problem.

In 2008, 36 million people died globally of NCDs and this number is projected to increase to 57 million by the year 2030. A factor that comes as a surprise to many people in high income countries is that low income countries are really hardest hit by these diseases and the epidemic is fueled by poor nutrition, alcohol, tobacco use and physical inactivity, particularly in urban areas.

Last year in September, the U.N. had a high level meeting on NCDs to try to develop a global action plan. This slide demonstrates rising rates of death due to NCDs in South Africa, both among men and women, and you can see that rates of stroke, heart disease and diabetes and hypertension are steadily rising. HIV is occurring in a milieu where NCDs are also prevalent. This is part of the intersection that I will be talking about.

I'm going to cover in my remaining time some information about the epidemiology, pathogenesis and some interventions for NCDs and HIV. I draw you attention to a

symposium that follows this session that will go into much more detail about many of these topics that I'll highlight.

Several studies have shown that in treated HIV infection, patients with HIV are higher risk for several non-communicable diseases and these include cardiovascular, non-AIDS cancers and while not a traditional NCD, osteoporosis, diabetes, frailty, also not a traditional NCD, cognitive disorders, chronic liver disease, more recently COPD and chronic renal disease.

Now with improvements in antiretroviral and reduction in rates of opportunistic infections, it shouldn't be a surprise that NCDs and non-AIDS related deaths are accounting for half of deaths for all people treated with HIV. Yesterday, Judith Schouten in a session on complications reviewed some data from a recent prospective study that looked at the clustering of co-morbid diseases in people treated with HIV disease compared to an HIV-negative control groups matched for age.

So you can see here on the green bars, these are the percentage of people with no other co-morbid conditions and as we age, that number gets smaller, but as we age with HIV, the decline falls off more quickly. I would also point out, especially among those over the age of 65, the percentage of people who had two or more co-morbid conditions was significantly higher.

Now this is not a phenomenon limited to high income settings. These data from Bill Wester from Botswana compared the rates of non-communicable diseases and ART treated patients in a cohort in Botswana compared to data from the U.S. and you can see higher rates of NCDs overall and particularly cardiovascular disease and cancer occurred at higher rates.

What contributes in the setting of HIV to the risk for NCDs? I'll talk about lifestyle factors, how the virus and the immune system may contribute and antiretroviral therapy. I'm going to focus my comments to in the setting of treated HIV disease.

Let's talk more about the pathogenesis and the virus and the immune system. Normal aging and abnormal aging is associated with progressive changes in the immune system, so putting HIV aside, as we age, we lose naïve t-cells, there's a reduced proliferative potential of those t-cells, there's expansion of senescent t-cells and there's increased production of cytokines like IL-6.

There's also monazite function that's altered with normal aging. These changes also occur in HIV infection, both treated, mostly untreated, but also persist to some degree during treated disease and that's led many people to wonder whether aging with HIV is a double hit to the immune system and whether these changes many underlie some of the chronic diseases that we're seeing occur.

In untreated HIV disease we have the loss of immune regulatory cells, thymic dysfunction, co-infection that proliferate HIVs replicating and importantly early in the disease, there's loss of gut mucosal integrity leading to the ability of bacteria that are normally in the gut to translocate into the circulation.

When ART comes along, we mitigate many of these processes, but not completely and this may be a factor that depends on when ART is started. The defects in t-cells regenerative protection persist, loss of immune-regulatory function, CMV and other co-pathogens may persist at low levels and this phenomenon of microbial translocation.

These factors all together conspire to cause chronic inflammation and immune activation, which then in turn can cause increased turnover and lymphoid fibrosis and immune exhaustion and possibly increase risk of malignancy, can cause tissue factor expression and clotting, coagulation disorders that could increase the risk of coronary disease and stroke and could cause altered monazite function cytokine secretion that can lead to a phenomenon known as inflammaging that could lead to atherosclerosis and osteoporosis.

Just a few examples of some data in this area: this is a study that looked at microbial translocation, levels of mucopolysaccharide a measure of levels of bacterial products in the plasma in patients with HIV compared to controls. You can

see that the HIV-positive patients have higher levels of LPS and even those who are suppressed on treatment still have a slightly persistently higher level.

Another potential marker of microbial translocation is called soluble CD14 and this is measure of monazite activation in response to LPS. In this study from the Insight Network, they found that those with the highest levels of soluble CD14 had an increased risk of death.

What about the role of antiretroviral therapy? Here I want to pause for a minute before I talk about specific toxicities of individual drugs to remind us all of the clear benefits of treating HIV disease. We saw yesterday from the HPTN 052-ACTG 5245 collaboration, the benefits of the starting treatment between the CD4 count of 350 and 550 and overall trend of reduction of a range of events, when secondary events of tuberculosis and serious bacterial infections were included, the benefits of early treatment were clear.

Now it's interesting to know that the rate of non-AIDS events in this study was very low and did not differ between the groups and I think this highlights the fact that these events may take years to develop are going to increase rates in older patients.

We have seen benefits of antiretroviral therapy on the risk of NCDs using surrogate markers so when we start ART, vascular function improves and many studies have shown

improvement in renal function, when it's abnormal to begin with.

The next few slides I'm going to show you, many examples of possible contributions of individual drugs to risk of specific diseases and I'll start with cardiovascular disease. I'm not going to review these in great detail, but just to highlight that there may be differences between individual agents and their contribution to different diseases, particularly a boost in protease inhibitors, a risk for MI, controversial data between Abacavir and the risk for MI and then some suggestions that Tenofovir may actually reduce the risk compared to other drugs.

Bone disease is another unique chronic complication to HIV disease and there may be a specific role of drugs when we start antiretroviral therapy, there's an initial decline in bone density that stabilizes. Some studies suggested that PI-based ART may have an independent role, although that's not a consistent finding. Exposure to Lopinavir/ritonavir in one large observational study was associated with increased risk of fracture risk as was communitive exposure to Tenofovir.

In addition Tenofovir has been shown to reduce bone density in several studies to a small degree of uncertain long-term clinical significance. Finally, there are associations to Tenofovir exposure and decline in renal function, again, particularly among patients who have other risk factors and

differences in the drug's abilities to cause increases in lipids and here the example is Fosamprenavir and Lopinavir and compared to other drugs.

Then finally, Stavudine, probably a drug that's still used by more people around the world, is associated with dyslipidemia, peripheral neuropathy, lactic acidosis, lipoatrophy and mitotoxicity, which may underlie the risk for long-term chronic diseases.

What about host factors? The role of genetics and lifestyle? Tobacco use is a very, very important cause for non-communicable diseases. It increases the risk for cancer, cardiovascular disease, bone loss and neurocognitive function loss. It's highly prevalent in many HIV populations and in the U.S., cohorts estimate 40-percent smokers, which is twice the rate in the general population. There are high rates in European cohorts and this is a concern in low, middle income countries as well. One study actually found that smokers had a reduced response to ART compared to non-smokers.

What about diet? I was fascinated to learn that the content of one's diet might actually have an effect on rates of microbial translocation. In studies in HIV-negative volunteers, a high fat was associated with higher levels of LPS, a measure of bacterial translocation and IL-6 compared to a diet of the same calories without the high amounts of fat. Dietary fat and cholesterol intake have been studied in

patients with HIV an higher dietary fat has been observed compared to control groups in at least one study.

When they looked at people that had a higher fat diet got more lipid increases on treatment, they found that this actually was true and then interventions that reduce fat intake were associated with improved lipid levels on ART.

Finally I'm going to focus on interventions in the last few minutes here. Primary disease prevention, research priorities and health system strengthening. First of all, we need to remember that early diagnosis of HIV and prompt entry into care is going to be an important component in reducing the long term risk for NCDs. We need to screen and monitor for these diseases and identify those patients who may be at highest risk. The Ryan White care model for in the U.S. has been the medical home for HIV disease and we have to be sure that that's not dismantled. [Applause].

Dietary education is also important, reducing saturated fat and reducing salt intake. Smoking cessation interventions need to continue to be something we push for. In some countries taxing tobacco has been very effective in reducing the rates of smoking.

Earlier start of ART may have an important contribution to long term risk, but we still need to define the impact of varying early ART on NCD risk. Then importantly, we need to tailor our drugs to reduce the risk of these diseases over

time. In order to do that, we have to continue to study how different drug regimens vary in their contributions to these problems. Finally we need to expand the use of safer ART drugs globally.

Exercise is also an important intervention. Regular aerobic and resistance exercise increases blood pressure, reduces osteoporosis, and improves neuropsychological health. Wondering why you're feeling a little cranky after being here for five days? This could be it.

It reduces risk of depression, decreases fatigue, improves quality of life and risk for metabolic syndrome. There have actually been recommendations made for exercise in people with HIV over the age of 50. This includes aerobic exercise three days a week for 20 to 40 minutes, stretching and resistance training. Resistance training does not require fancy equipment or membership at a gym. It turns out you can use your own body weight as the resistance.

Research priorities in this area we need to identify and test interventions this burden of chronic disease and treated HIV and these would include interventions of inflammation, immune activation, possibly to treat co-infections and to address specific disease risk factors like dyslipidemia.

Finally, we also need to evaluate treatments for NCDs in the setting of HIV. There are very important drug

interactions that we have to take into consideration as we go down this path. On Monday afternoon there was a great symposium that talked about inflammation and immune activation in HIV that highlighted much of the work that's going on, looking at these interventions to reduce these problems. There were interventions targeting microbial translocation and toll-like receptor inhibition. There were also yesterday discussions of the affects of aspirin on reducing platelet activation.

Many of you might also have noticed the recent study using chloroquine in patients with untreated HIV disease. I think it's important to reflect that treated HIV disease and untreated HIV disease are very likely to be different. In terms of infrastructure development, I mentioned screening and treatment – integrating these together – and I think that HIV programs can serve as a model for managing other chronic diseases in other low and middle income settings; a topic our next speaker will talk about in more detail.

Lessons learned from the scale up of HIV can be applied to the expansion of care for NCDs in these settings. There were many examples of this presented at this meeting: In Uganda, screening for HIV and diabetes, hypertension all at the same time. So the NCD and HIV worlds are often competing against each other, and I think the secret is to gang up on the problem rather than each other.

In conclusion, I hope that I've been able to illustrate that HIV and NCD epidemics are colliding on a global scale; that aging with HIV appears to increase the risk of some of these diseases. We need continued investment in drug development to identify the safest possible long-term options because we're going to be treating millions of people for millions of years.

Integrating the screening and care into HIV settings to prepare for the future, we also need to enlist a new generation of health care providers to take on the challenge of HIV in the years to come, using this HIV platform as a model in low resource settings.

I think our failure to address these problems could lead to an erosion of the benefits of ART in the years ahead, but I think it is absolutely possible that we can make healthy aging with HIV an achievable goal. [Applause].

So I'd like to pause for a moment to acknowledge the considerable input and guidance that I received in preparing this talk from Peter Rice from the University of Amsterdam and from Peter Hunt at the University of California in San Francisco. They shared slides and ideas and helped me figure my focus.

I also want to thank the individuals listed on this slide who provided input: John Brooks from the CDC, Steve Deeks from UCSF, Jill Berninghausen from the Africa Center at

Harvard, Lisa Hirschhorn, also from Harvard, Bill Wester from Vanderbilt, and I want to acknowledge the outstanding work that Jules Levin has done advocating for the importance of aging with HIV as a priority. [Applause]. Thank you very much for your attention. [Applause].

FEMALE SPEAKER: Please welcome Dr. David Wilson, Global Aids Program Director at the World Bank. [Applause].

DAVID WILSON: Yougan Pillay is the Deputy Director General for Health in South Africa, responsible for policy making, guiding implementation and monitoring of national programs in HIV, TB, maternal and child health and women's health.

He is currently facilitating the implementation of a national program to re-engineer South Africa's primary health care system. Yougan has a PhD from Johns Hopkins University and has contributed numerous journal articles including papers on HIV financing and HIV/TB co-infection.

He's also co-author of the textbook on international health, *Global Health in a Dynamic World.* The title of his talk is: Optimization, Effectiveness and Efficiency of Service Delivery: Integration of HIV and Health Services. Please join me in welcoming Dr. Yougan Pillay. [Applause].

YOUGAN PILLAY: Good morning, everyone. I'd like to say how glad I am that this is not Toronto. For those of you in Toronto, you'll know what I am talking about. Nothing

against Toronto as a city though; it's a beautiful city. Let me tell you why I'm glad it's not Toronto.

In South Africa, in the last 20 months, we have tested for HIV 20 million South Africans. [Applause]. Since we've started the anti-retroviral therapy in South Africa in 2004, admittedly through a court of law injunction against the government, we have now cumulatively 1.7 million people in treatment. [Applause].

Our transmission rate – vertical transmission rate – was eight percent in 2008. The latest figures we have, for 2011, is 2.7 percent. [Applause]. From May of last year to May this year, we have done half a million voluntary medical male circumcisions. [Applause]. The proof of the pudding for us is in people living longer. As John Borr [misspelled?] reported in this conference, people are living longer and Judith showed John's slide.

Between 2003 and 2011, the average life expectancy in a community in KwaZulu-Natal – one of the provinces in South Africa – increased from 52.4 years to 60.6 years, an increase of eight years. [Applause].

So I'm glad I'm not in Toronto. On behalf of Elly Katabira and IAS, I'd like to salute all the health workers all over the world, but especially those in sub Saharan Africa and those in South Africa. Without you we would not have been able to reach these towers. [Applause]. Thank you very much.

So the question still remains, how do we do more, how do we do better and how do we do smarter? I don't always agree with Bill Gates, but I do agree with what he said on the panel the other day: that we do indeed need new tools and we do, indeed, need more money. However, we also need more efficiency.

However, you cannot get more efficiency without having the supplies. Tony, I heard this morning from my Chief Director responsible for TB that there's a global shortage of cartridges for gene experts. South Africa has the largest number of gene experts in the world, but we have a shortage of cartridges. So there's not much you can do without cartridges.

We've also recently experienced shortages of Ebakleva [misspelled?] and TDF. There's not much more you can do, in terms of efficiency, if you don't have the drugs. So as we scale up to 15 million and beyond by 2015, we must ensure that he diagnostics and the drugs are available. [Applause]. Now let me turn to my presentation for real. Those were just preliminary comments I wanted to make.

I stand here as a really proud African today. If you look at me you might not think I'm African, you might think I'm from the Indian south continent, but really I am from Africa. [Laughter] [applause]. The president of Benin and the chairperson of the AU said this a few weeks ago.

"Dramatic progress made in access to HIV treatment in Africa during the past decade has transformed the lives of numerous families, strengthening the social fabric and increasing economic productivity. We can state that we have new hope, but there is no room for complacency.

I'm working closely with all African leaders to develop a roadmap for shared responsibility, with concrete milestones for funding, for access to medicines that must imperatively be produced locally in Africa, for enhanced regulatory harmonization and improved governance."

There are any number of examples of corruption in Africa, as elsewhere, and clearly the leadership in Africa is now signaling the time to stop corruption is now. I'm also standing as a proud South African.

In 2004, Anglican Arch Bishop Njongonkulu Ndungane said the following, "These were the dark days in South Africa. It seems now as if the health department, of which I'm a member - now, as I was then – is once again dragging its feet when it comes to implementing a comprehensive and efficient strategy to combat the disease." He's talking about HIV. "Yet the reality on the ground is that HIV/AIDS is killing mothers, fathers and children. HIV and AIDS will not go away if we ignore it. It is getting worse."

Now one of our major critics in South Africa has been Mark Heywood, who is the Director of Section 27. I think many

of you know Mark as a fairly well known AIDS activist. This is what Mark said to me before I left home last week, and I quote: "For many years UNAIDS has talked about the vital importance of political leadership in the HIV epidemic as one of the key components to an effective response."

This was something civil society also fought for in South Africa. Today, there is now no question that in Dr. Aaron Notsoaledi the Minister of Health, we have great political leadership. It is this leadership that is mobilizing society, and now beginning to show a dramatic reduction in vertical transmission of HIV that is being announced today. [Applause].

My presentation will really be in three parts. The first part will talk about optimizing spending alongside increasing funding commitments, the second will talk about country ownership and the third will talk about what we need to drive this change.

This is a slide that Gottfried presented yesterday, and I guess we don't have to deal too much with whether or not we move to a city for 500 when WHO presents its next clinical guidelines, but we move to test and treat.

The key message here is that we will be putting larger and larger numbers of people on treatment, which means we will have to have a health system that can sustain – and a social system that can sustain – large numbers of people that are

chronically ill. I think Judith made the point very adequately that we would need to ensure that we have a plan to deal with chronic diseases.

Efficiencies, we think, can be examined in three broad categories. One is element of efficiency, which means increasing spending on high impact interventions, second is technical efficiency; improving the efficiency of direct service delivery and third is structural efficiency, which is reducing spending on indirect costs.

We know that many of the large funders, when they have international implementers, will come with high degrees of technical skills, and also come with high degrees of overheads. So one way to reduce indirect costs is to reduce overheads, and we need to look at how we reduce overheads. [Applause].

In terms of country ownership, we need to figure out where the money is going. You will remember Secretary Clinton arguing that we need to follow the virus. Following the virus often means figuring out who you need to treat, when and how. Here's a slide from Patrick Osewe, from the World Bank, who did some work in South Africa in KwaZulu-Natal on the distribution of HIV spending.

Patrick tells us in KwaZulu-Natal, 55-percent of total HIV expenditure was in treatment; a large 13-percent was in voluntary counseling and testing. Clearly we would need to

figure out how to squeeze additional efficiencies from at least these two buckets.

If you look at Thailand, Thailand, in the latest report that they provided for the Asian Commission on HIV, suggested that 80-percent of total expenditure in Thailand is treatment related. Treatment is very important, and this is a slide that has been shown a few times already, but because it's from my country I feel I should show it again. We know treatment works at a population level, so it's very important to find people and treat them; both for their own sakes and for the sake of the population.

I want to dwell a little bit on the Match Study, which was done by CHAI, in a number of low-middle income countries. This study shows the fairly significant variation in cost per patient treated per year in Malawi, Ethiopia, Rwanda, Zambia and South Africa. This begs the question, should there be a difference?

If so, how will we explain the difference and is difference justifiable? It also begs the question of what should be the norm. What should be the average cost of patient treated? According to PEPFAR and Ambassador Goosby, it should be around $300-$330. According to this study, it averages out to $200.

The key issue though, is what is counted and how. Should the benchmark be South Africa at almost $700, or should

the benchmark be Malawi? That all depends on the regiment one uses and the number of labs one needs. So in the United States, for example - which has moved quite quickly to test and treat in terms of the HSS treatment guidelines – every three months a patient should have a viral load done. This is not going to be possible in a country like Malawi, and therefore, we cannot add that cost in.

So depending on your treatment regiment and your treatment guidelines, you might have highly variable costs. The point of this slide, however, is not quite that and to set international benchmarks. The point of the slide is to try and figure out for each country what the correct mix of costs are to give you the best outcomes.

And to their credit, the Match Study did look at outcomes, and this slide shows – the second slide shows – this slide shows what basically what drove the costs. You can see that if you use D4-T, your costs will be lower because the drug costs less, but if you move quite quickly to TDF your costs will be much higher. The countries that are moving to TDF will, of course, have higher costs, so treatment regiments do drive costs up or down.

This slide suggests, from the Match Study, that not withstanding the input costs and the variability in the input costs, there seems to be a suggestion from the Match Study that we can improve outcomes at very little additional cost. And

that we can, by improving the efficiency of our service, increase value for money.

I do think that program managers like myself need to spend more time thinking about how the service delivery arrangements can be changed to get maximum impact on efficiency. Integration is possibly one of the key ways of achieving increased value for money. So I'm glad I'm following both Tony and Judith with respect to both TB and other chronic diseases.

There are a number of ways in which resources can be tracked, and one needn't go in to all of the ways, but I think there are a number of methodologies that exist. We do not have to wait for new methodologies to track resources. Admittedly, it would not be perfect because our data collection systems are not perfect, but we have some good examples that give us some ideas of what the unit costs are.

I think it would be wise of us to start using these at both facility, district, provincial and national levels. It's only by using this that we will be able to squeeze additional efficiencies from the system and ensure that the way in which our service delivery platform is designed does, in fact, embody all of the tenants of integration that both Tony, with respect to TB and Judith, with respect all the other NCDs have commented on.

I think we must acknowledge that we don't have very accurate knowledge to ensure maximum efficiency, but what we do have I think we can use to ensure that we have a prioritized and well-costed set of national and sub-national TB and HIV plans at minimum. I'm quite happy to announce, Tony, that South Africa for the first time, since the 1st of December, 2011, has an integrated TB, HIV and STI plan.

I think that implementing that plan [applause] going forward will give us maximum benefit on the integration side. Judith, I'm also happy to report that we have three pilot districts in the country that are piloting an integrated model for chronic disease management, and we will be happy to share those results in Australia.

So the last part is driving change and what will that require. The first question is why aren't national plans always evidence based and prioritized? Well, there are a number of reasons, and I saw it first hand when we were developing our own national plan. There's a lot of inertia to continue funding existing programs despite knowing that for some things there's insufficient evidence. For some things, we will have to continue do it even if there's insufficient, randomized from trial to trial evidence, but there's observational evidence we can use.

There are a number of constituencies in both HIV, TB and now growing, as Judith mentioned, with non-communicable

diseases. It often turns out that you develop a shopping list or a laundry list of priorities rather than a list that can be justified. A big bug bear, and a continuing challenge despite the Paris declaration, is lack of alignment of strategic priorities across key partners. Can I make a plea to our major donors? Please work with us to ensure alignment against national strategic plans. [Applause].

Finally, and here again I agree with Bill Gates, is that I think we still don't have enough research on what is working in countries. However, it will take strong political leadership and the engagement of all stakeholders to manage a well coordinated strategic planning process that produces an evidence based prioritized national plan that is then well implemented.

Now here's the gap, ladies and gentlemen. With the best will in the world and with increased domestic investment, we will still be significantly short of what we need to reach the targets that Gottfried suggested yesterday we would need to reach. So we would have to be more efficient. We have to optimize, we have to integrate. I mean they really are no brainer. The question is how to do these things.

Courtesy of Elly and IAS, there was a consultation in April this year in Nairobi with health professionals to try and figure out how do we achieve E-squared. E-squared is just efficiency and effectiveness in national programming. That

meeting basically argued that E-squared is necessary, but not sufficient to drive change. What we do need are optimized service delivery models, harmonized and action that involves various actors, the need to identify bottlenecks at the lowest level and to make equity concerns more explicit.

In terms of research, the group that met in Nairobi agreed that we need to develop and consolidate a research network. Even in my country there's research popping up everywhere. Throughout the conference and this morning you heard a number of examples of research being – piece of research being done in South Africa, for example. That's a good thing.

We need to figure out how to make research work for us as quickly as possible. We need to develop and sharpen definitions and the research tools and we need a greater focus on research on efficiency and effectiveness including research that measures quality of life and cost benefit, and we need more research on sustainability.

The group in Nairobi also called for a new global compact, and I'm glad to say some of these things are contained in the Washington declaration: That countries should and must take the lead, and partners must be pulled into alignment, that resources should be reallocated - regardless of the source - according to the country's needs and priorities for greater and

more sustainable results, that partners in countries must fill the investment gap together.

We had a lot of discussion on global solidarity and the fair share. The key question is how do define the fair share and get countries to commit to making an investment. Clearly, programs need to be implemented as efficiently as possible, without parallel structures - so Tony, I'm very glad that you spoke about TB/HIV integration - without stand alone services or higher than necessary program costs.

So ladies and gentlemen, in conclusion, I'd like to thank the organizers again very much for this opportunity to present on behalf of all my compatriots from Africa and South Africa; and thank in particular for helping me develop this presentation: Matson, Elly, the participants of the Nairobi IAS consultation, my colleagues from CHAI – who requested not to be named, I'm not sure why [laughter] – colleagues whose work I used, people I work with, especially the front line health workers. Thank you all very much. [Applause].

TEGUEST GUERMA: This ends the plenary session. I would like to thank the three presenters for their excellent presentations, and I would like to thank all of you for your participation. Thank you. [Applause].

[END RECORDING]