

**4th IAS Conference on
HIV Pathogenesis, Treatment and Prevention
Plenary: The HIV/Life Cycle: Understanding HIV Pathogenesis,
Accelerating ARV Rollout and Exploring the Clinical
Implications of Ageing
International AIDS Society and
Australasian Society for HIV Medicine
July 23, 2007**

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MALE SPEAKER: – and treatment. We are here with my friend John François [misspelled?], chair of the INRS, the National Agency for Research. Our task is here to announce the three award winners of the IAS/INRS research prize at this conference. The prize of \$3,000 US dollars recognizes young researchers who demonstrate excellence in the area of research programs related to the scale up of prevention and treatment services in resource-limited settings. The presenting authors of the winning abstracts must be under 35 years of age and must be a citizen of a low or middle-income country. As well, the research being considered for the award must have been carried out in a non-OECD country. The young investigators honored by this prize represent the real hope that individuals from areas of the world most impacted by this disease will contribute significantly to eradicating it. In addition to the price and certificate, prize winners will also receive a complimentary one-year IAS membership. We hope they will remain as such. John François?

JOHN FRANÇOIS: This is a further analysis prize to be present. The inaugural prize was presented in Rio de Janeiro two years ago. The prize was money was donated by the INRS, the French National Agency on AIDS Research from [inaudible]

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following the [inaudible] conference in Paris. The three 2007 award winners are: Demetro Kovalis Key [misspelled?], Ukraine, for his abstract development of small molecule inhibitors of [inaudible] interaction as a new anti [inaudible]. The second winner is Hapalo Basinero [misspelled?] [inaudible] for his abstract [inaudible] of clinical and immunological criteria [inaudible] virological [inaudible] for the first time of treatment. It's a Ugandan experience. For the first prize, [inaudible] is accepting for Lei Yin [misspelled?] from China for his abstracts [inaudible] of HIV and hepatitis C viruses among injection drug users in China, a three-year [inaudible] study. Please join her in congratulating these impressive young researchers for contributing their talent in the response to this epidemic.

[Applause]

JULIO MONTANER, MD.D., F.C.C.P., F.R.C.P.C.: Good morning, everybody. My name is Julio Montaner. I'm the president elect for the International AIDS Society. It is my pleasure to open the first plenary today and introduce our first plenary speaker, Dr. Debrework Zewdie, who is going to be talking on understanding the task of antiretroviral rollout and research issues in the developing world. Dr. Zewdie has a very extensive trajectory in the field of HIV and AIDS. She is the Global HIV/AIDS Program director in the World Bank's UNAIDS

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global coordinator and representative on the board of the Global Fund to Fight Tuberculosis, Malaria and AIDS. Prior to this position, she managed the AIDS Campaign Team for African and led the team responsibility for the 1 billion, multi-country, HIV/AIDS program for African. Before joining the Bank in 1994, Dr. Zewdie was Africa's deputy regional director for Family Health International's AIDS Control and Prevention Project in Kenya. Previously, Dr. Zewdie had several research management and teaching positions focusing on public health issues. While in Ethiopia, she was deputy director, then acting director, of the National Research Institute of Health. Dr. Zewdie also established and headed the Referral Laboratory for HIV/AIDS in Ethiopia. She served as program manager of Ethiopia's AIDS and STD Prevention and Control Program and taught immunology at Addis Ababa University.

She received her PhD in immunology from the University of London and was Senior MacArthur Fellow at Harvard University School of Population and Development Studies. Dr. Zewdie has published in excess of 100 peer-reviewed papers and book chapters on a variety of subjects related to this matter. We welcome her to talk about understanding the task of antiretroviral rollout and research issues in the developing world. Dr. Zewdie?

[Applause]

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DEBREWOK ZEWDIE, PH.D.: Julio, thank you.

Distinguished guests, chairs, ladies and gentlemen, let me first of all thank the IAS for giving me this opportunity to talk to you today. I am honored.

In 25 years of the pandemic, HIV has spread to every country on earth. Globally, up to 40 million are living with HIV, yet we don't face this epidemic without tools. HIV is preventable and AIDS is treatable.

This morning, I would like to discuss how research has been critical in developing our understanding of our epidemics and our response to them. In my presentation, I will cover the current status of treatment access globally and progress to universal access, the role that research plays in treatment rollout, some challenges to conducting research in developing countries, areas of priority research that need urgent support, and then I will finish with recommendations for action.

In the north, after the efficacy of ART was demonstrated in 1996, treatment discourse was dominated by the belief that ART was too expensive, too demanding of scarce health systems resources and simply too complicated for Africa to manage. Just five years ago, only 300,000 were receiving ART globally and this was dominated by Latin American, mainly Brazil. However, a handful of dedicated researchers in Haiti, South Africa and elsewhere demonstrated that treatment was

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feasible in the poorest of settings, that adherence was at least as high as seen in western cohorts and the fear of massive drug resistance being fueled by these programs was unfounded. This research generated evidence that could not be ignored. It led to the 3 by 5 Initiative, launched by WHO, UNAIDS and partners with the goal of providing treatment to 3 million people in developing countries by 2005.

Africa was galvanized into action. Across the continent, AIDS treatment expanded on a scale considered impossible a few years before. Notwithstanding the scale of the unmet need, treatment coverage in many African countries exceeds treatment coverage in Asia. Despite having much smaller epidemics and greater resources, treatment coverage in China, Indonesia and India lags behind that of Rwanda, Malawi and Swaziland. Locally relevant operational research is essential to expand treatment coverage in contexts where epidemic patterns and capacity vary widely.

In the most recent report of WHO, UNAIDS and UNICEF, we see encouraging progress. Global treatment coverage now exceeds 2 million people or 28-percent of those in need, compared to only 7-percent in 2003. But a closer examination of these figures reveal a more complex story. Wide variations in ART coverage exist between regions in Africa, particularly coverage of children lags significantly behind that of adults.

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However, access to treatment by women, which previously was disproportionately low, has improved. This figure shows women as a percentage of all adults receiving antiretroviral therapy versus the expected percentage in selected countries in 2006. In most instances, coverage is broadly in line with regional HIV prevalence [inaudible]. Despite this success, it is clear that significant challenges remain before our goal of achieving universal access.

I'll now turn to the pivotal role that research plays in reaching this goal. There are four distinct areas in which research influences treatment rollout and program sustainability: Through basic science and the discovery of new drugs; by understanding the determinants and dynamics of the epidemic; through operational research to refine treatment strategies, evaluate interventions, guide implementation and inform programs for maximum effectiveness; and by cost-effectiveness research to provide essential evidence for policy development and sustainability. Of these, I would like to concentrate on operational research and cost effectiveness.

There are two useful definitions that cover the breadth of operation research: Learning by doing how to do things better in the real world and generating evidence specially to inform operations. In the field of development, operational research is used to refine programs, to understand what is

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working and what is not, to adapt generic approaches to country-specific environments, and to inform the monitoring and evaluation of programs. Cost-effectiveness research aims to measure outcomes against cost. Both of these approaches play a critical role in the rollout of antiretroviral therapy.

When we consider the rollout of antiretroviral therapy towards universal access, what is the potential role of research and how well is it funded? Antiretroviral therapy is lifesaving, but also complex to administer, brutal and prone to toxicity. Operational research is essential to improve the quality of patient care. Too often, we needlessly repeat mistakes from which there is abundant evidence to protect us. We need appropriate delivery of first-line therapy to maximize its early safety and longevity and to optimize sequencing to second-line therapy, as well as accurate indicators of treatment failure, which all directly affect treatment sustainability. Research builds local capacity, providing a career path and opportunities for researchers who would otherwise be lost to developed countries. The impact of those key individuals is wide-ranging. Not only do they perform research, but their expertise contributes to training programs and centers of excellence in clinical care. A research program builds long-term links with overseas institutions, bringing external technical capacity and funding. Supporting the

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research also builds systems of [inaudible] review, monitoring and quality control that have brought benefits for health services. Research provides the evidence essential to guide our strategic planning and demonstrate program cost effectiveness and efficiency. Without evidence that programs are efficiently delivering services and have demonstrable outcomes, the funding for those programs may wither.

Consider one example of operational research in treatment services in Haiti. In some countries, the introduction of HIV programs has reportedly the health system and diverted scarce human resources away from other disease priorities. This is not always the case. The introduction of services for HIV/AIDS can have a very positive effect, as was demonstrated in Haiti where the treatment program led to an expansion of primary healthcare facilities into communities that had very limited access to health services. Over the period of the intervention, patient visits for AIDS care rose, but so did visits for a number of untreated primary healthcare issues, including perinatal care and vaccination of children.

The AIDS treatment and research program has been the vehicle of general strengthening of the local health system. Conversely, there are abundant examples of where failure to support research targeted to address operation needs has resulted in delays and misdirection in program implementation.

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There is not better illustration of the importance and urgency of research than male circumcision. It is the world's oldest and most common surgical procedure and ecological studies have long suggested that male circumcision is a major factor in variations in the HIV/AIDS epidemic in Africa. Metaanalysis showed that male circumcision was associated with a 60-percent reduction in HIV. So why did the world have to wait for 25 years into the epidemic for the randomized trials in South Africa, Kenya and Uganda to show that male circumcision reduces transmission by 60-percent? What other critical information on prevention and treatment are we missing that we have failed to support through operational research?

With that in mind, I'll turn now to the key challenges that face research in AIDS treatment in the developing world. In our efforts to deliver treatment services today, our most difficult challenge is not funding. It is the limited health system capacity in the countries of highest disease burden, in particular the desperate shortages of doctors, healthcare workers and researchers who would not only deliver treatment services, but would also conduct the locally relevant operational and clinical research required to inform them. Many of the countries that most need trained healthcare workers are [inaudible] exporters of doctors and nurses. These data, collected by the World Bank, show the numbers of doctors

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trained in developing countries and how many of them have immigrated to currently work in the developed world. In my home country of Ethiopia, for instance, we have fewer than 2,000 doctors. That is about 3 for every 100,000 people. Yet, 578 of these currently work overseas, mainly in the US. In Papua New Guinea, which is experiencing one of the worst HIV/AIDS epidemics in this region, there are only 284 doctors, fully half of which are working outside of their country, the majority in Australia. Indeed, Australia itself is a substantial net importer of doctors, accounting for 6,500 out of 57,000 from these countries, more than the United Kingdom.

In addition to the scarcity of human resources, treatment rollout and research is severely limited by the absence of the creation of key infrastructure. The clinical researcher attempting to conduct a study is faced with tablets and diagnostic kits trapped behind Customs or lacking specialized logistics required to bring them to the trial site. Patients commenced on therapy need laboratory monitoring, but frequently this is either not available or the internal and external systems for quality control and proficiency testing are not in place. Appropriate pharmacy storage with climate control, stock inventory and other systems taken for granted in developed countries simply do not exist in many countries. Patient care, including research [inaudible] and infectious

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waste that must be properly disposed of, but often there is not capacity to do so.

When we look at the world through the lens of HIV/AIDS, two great geographic disparities – prevalence and mechanism of transmission – are immediately apparent. This map shows the countries of the world, drawn proportionately in size to the population of people living with HIV. This world is dominated by the countries of Southern Africa, where two-thirds of all people with HIV live and where all countries with adult prevalence over 10-percent are found. Also consider how diverse the sources of transmission are globally. Our treatment programs must reflect this remarkable diversity in epidemic scale and vulnerability.

In the last 10 years, despite dramatically increased commitments for HIV programs, little has changed in terms of resources allocated to research. These figures do not address treatment specifically, but look at proportional locations to research overall. The World Bank's multi-country AIDS program for Africa estimates that from 2003 to 2005 funding spent on research and administration was 8-percent of total funding committed in that period. Administration may have contributed to a substantial percentage of this and these data research were defined broadly, including situational analysis and some surveillance. The Global Fund, which encourages the allocation

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of resources for operation research received applications with operational research components in only 54 out of 358 applications in rounds 1 through 5. Although 28 out of 88 countries included operational research requests in round 6, the overall total requested for operational research remains limited at \$24.2 million. In 2007, [inaudible] estimates spending at \$32 million in public health evaluation.

Therefore, firstly, resources allocated to research by the three major funding agencies are insufficient. Secondly, even when funds are specifically made available for research, such as in the case of the World Bank and the Global Fund, they are often not used because funding agencies have not directly tackled the immense constraints to research.

Consider the doctors working for minimal salary with a huge patient load in a developing country. What are their incentives to work in clinical research rather than private clinic where they can earn money for survival? What career structure is there to support clinical research in developing countries? It is scarcely surprising that research funds are underutilized.

I would now like to consider some priority needs for research and global progress to universal treatment access. They are: Research to optimize treatment approach and effectiveness; research into better integration of HIV with

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other services; research to understand and overcome the social, political and cultural barriers that hinder access to therapy; research that will enable better integration of new therapies, technologies and guidelines and their development; importantly, research into cost effectiveness and program sustainability. By the end of 2006, 42 low and middle-income countries were providing treatment to at least the global average of 28-percent of those in need. This is unquestionably a tremendous humanitarian and public health achievement, but what about those who are not yet on treatment, the people who need it now who will die without it, which is 70-percent of people in South Africa and Ethiopia? How can we do better in expanding our coverage, preserving the efficacy of our first-line regimens for as long as possible, managing toxicities and reaching distant and poor populations? With treatment coverage of children half that of adults, what can we do to create incentives for research to improve pediatric formulations and clinical management of HIV disease in children? In Africa's generalized epidemics, these operational and clinical research questions are quite simply indispensable if we are to achieve our goal of universal and equitable treatment.

Integration of HIV in the broader range of health services is not only essential, but is cost effective. Tuberculosis is the most common AIDS-defining illness and

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between epidemics of tuberculosis and HIV, few [inaudible] in the high-burden countries of South Africa. Understanding and managing the synergies between HIV and TB will be critical to the success of AIDS treatment globally.

Consider these data from South Africa, which show the dramatically worsening changes of TB-free survival in patients starting antiretroviral therapy with more advanced immunodeficiency? When do we start antiretroviral therapy? Do we treat tuberculosis immediately or later? What are the community-level impacts of antiretroviral therapy on incident tuberculosis? It is essential that research, operational and clinical be supported to answer these questions and to develop better models for the integrated management of HIV, TB and other major co-infections.

Treatment poses different challenges in generalized and concentrated epidemics. In generalized epidemics, although stigma must be tackled, HIV treatment is offered to eligible clients from the general population. In concentrated epidemics, HIV treatment must be offered to marginalized groups such as injecting drug users, sex workers, men having sex with men and prisoners. The social, political and cultural barriers to members of these vulnerable groups accessing treatment are often complex and obscure. For example, there is overwhelming evidence that injecting drug users are not receiving treatment,

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even when they are eligible for it. The graph shows the disparity between the representation of injecting drug users among people living with HIV and the low number enrolled in antiretroviral therapy. Research is required into new approaches to motivate societies to protect and treat their most marginalized members and to provide treatment in a manner that does not exacerbate existing prejudices. New models of integrated care, including effective treatment for drug dependency, are urgently required to address this need.

Time and again, we return to the need for evidence, evidence for policy, evidence for programming, evidence for technical guidelines. Most countries have standard criteria for starting ART that are in line with WHO guidelines. The composition of first regimens is fairly uniform, but those for second-line regimens are much less so. A globally standardized approach to sequence ART regimens, informed by rigorous evidence and akin to the standards for TB management would in turn standardize and simplify individual clinical management, national procurement, global drug demand forecasting and treatment sustainability.

More than ever before, there are substantial international AIDS resources. However, the volatility and targeted nature of these resources present complex fiscal management challenges in countries with limited capacity. In

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this figure, trends in external HIV funding commitments are shown for selected African countries from 2000 to 2004. The surge in total international funding for HIV/AIDS response belies the instability of resources available at the country level. For example, funding committed jumped approximately 1,000-percent in Swaziland between 2002 and 2004. In some of these countries, HIV/AIDS money exceeded 150-percent of the government's total allocations for health and this trend has continued.

How do we help developing countries deal with the significant fiscal ramifications of this volatility in external funding? One key element that can be provided, but that very rarely is, is rigorous cost effectiveness research in national treatment programs. Understanding costs and demonstrating effectiveness are vital, both to long-term strategy planning and to accessing a sustainable, stable level of funding.

In summary, therefore, the rollout of treatment towards universal access has made great progress, but significant inequalities remain and the great majority of those who need treatment still do not receive it. Research plays a key role in the success of treatment rollout in informing treatment programs, building capacity and producing the evidence needed for strategy planning and sustainable funding. The key challenges to research include limited health system capacity,

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in particular human resources and infrastructure, the diversity of the epidemic and low levels of funding for research.

Priority research needs to include optimizing treatment approach and effectiveness, the better integration of services, understanding the social, political and cultural barriers to access, integration of new therapies, technologies and guidelines, as well as research into cost effectiveness and economic sustainability.

So, where do we go from here? I would like to suggest that three things need to happen. Firstly, funding for research, including creating an enabling environment for developing country researchers must increase to a significant proportion of international support for treatment. Secondly, effective north-south and south-south research partnerships must be developed and fostered. Thirdly, a shared prioritized agenda must be developed between those engaged in treatment research and those in treatment programming.

Let me explore these suggestions a little further. We at the World Bank fully support the Sidney Declaration's goal of increased investment in HIV/AIDS prevention and treatment research. We acknowledge that at the moment our own programs still fall very short of this. Consider for a minute that we succeed in implementing the declaration of international commitment of \$60 billion over the next 5 years. Let's suppose

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that \$40 billion will be allocated to AIDS, included \$20 billion for treatment. Although this is a best-case scenario, 10-percent of treatment funds would amount to \$2 billion for treatment research, \$400 million a year more than the annual allocation for international HIV research supported by the US NIH.

Secondly, we must recognize our shared goal. We want to reverse this lack of a research culture, we want to reverse the brain drain and bring our doctors home. We want the international AIDS response to support the research that will generate the evidence it needs through effective north-south and south-south partnerships. There are already highly successful examples in Africa and Asia, such as Uganda, Botswana and Thailand, of how research partnerships in clinical care can build capacity, foster international collaboration and provide training and career opportunities for local healthcare workers. We need many more such examples.

Thirdly, we need a prioritized agenda shared between the research community and HIV programs, so that research can address operational questions and HIV programs can integrate research into their core activities. We need to move away from the paradigm of treatment programs and treatment research being separate and independent. This model is simply unsustainable. Just consider an example of this association that is etched in

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my memory. The Rachi [misspelled?] STI trial in Uganda and the World Bank's Uganda STI project both took place in the mid-1990s. While working on the World Bank's STI project, we inadvertently learned that the Rachi trial had already established that many STIs were extensively resistant to some drugs on the [inaudible] drug list, yet the national program continued to buy the same drugs.

We need to implement new models for integrating research within programs, whether as an embedded part of the program design, as operational research works as part of program evaluation, or as a distinct program of research which is supported by the program with collaborating partners, as would be the case for randomized clinical trials.

We have come a long way, but we have also strayed from our goal. We started in the 1980s in the right direction – asking questions and doing relevant research, the fruits of which we see today. However, for the last decade our mantra has been “We know what to do. All we need is money.” While AIDS research continued in the north, AIDS activities in the south focused largely on scaling up research, which was neglected and grew disassociated from programs.

I would like to conclude with a personal example that's close to my heart as an African research working abroad. As a young scientist, I established a research laboratory in

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Ethiopia and trained a generation of a laboratory scientists. My colleague, Professor Mumbu [misspelled?], established a similar laboratory and training center in Senegal. Today, over 80-percent of all young Ethiopians I trained have left their homeland and the laboratory is reduced to a diagnostic lab. Yet, Professor Mumbu's laboratory flowered into one of Africa's great research and training centers. Why? The answer helps to eliminate the challenge of brain drain. Senegal and other centers of research excellence in Botswana, Kenya, Uganda and Thailand have enjoyed decades of peace and stability, which allowed them to build deep, enduring international research partnerships. In Ethiopia, as context of recurring instability, we couldn't attract long-term resources or retain skilled staff. Nor is this a problem limited to Ethiopia. It is very easy to forget how much we owe to the now withered research programs of the Congo, Cote-d'Ivoire and Zimbabwe. Effective, long-term research partnerships require stability and security. HIV programming is moving from an emergency response to the sustained delivery of comprehensive services integrated with and supporting the broad health system. Along side this evolution has grown a system of monitoring and evaluation that sets best practice examples in development. It is time for the system to come to grips with the complexity and the risk that characterizes the treatment of large populations

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of people living with life-long medication and to put in place systems of evaluation and mechanisms to generate evidence that directly addresses treatment outcomes. As research is supported, so will the capacity, the energy and the ownership that has been so desperately lacking start to flow back to the countries which has suffered most from this epidemic. I thank you. [Applause]

JACK WHITESCARVER, PH.D.: Good morning. I'm Jack Whitescarver from the National Institutes of Health, and it is my pleasure this morning to introduce our next speaker, Dr. Michael Lederman. Dr. Lederman, a clinical immunologist, leads a large clinical and laboratory research team that is exploring the pathogenesis of HIV-related immune deficiency and is testing strategies to prevent infection and to restore immune defenses. Dr. Lederman earned his MD degree at Mount Sinai School of Medicine. He has spent his significant career at Case Western Reserve University where he joined the faculty in 1980. He is the Scott R. Inkley professor of medicine and the director of the Case Western Reserve University Hospitals of Cleveland Center for AIDS Research, CFAR. The Case CFAR provides clinical and technological support to researchers working on AIDS-related projects at Case Western, at University Hospital Case Medical Center, Metro Health Medical Center, the Cleveland Clinic Foundation and several international sites.

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Dr. Lederman is the principle investigator of the Case AIDS Clinical Trials Unit. Dr. Lederman's group is also working in the critical area of microbicide research and has recently been selected to participate in the newly established Microbicide Trials Network sponsored by NIH. Dr. Lederman has had a successful and ongoing collaboration, since 1991, with the Joint Clinical Research Center in Kampala, Uganda and has an ongoing commitment to finding ways to translate research results to resource-constrained areas. His presentation today will focus on critical elements of HIV pathogenesis, the title How HIV Makes You Sick: Mechanisms of CD4 T Cell Loss and Recovery. Dr. Lederman? [Applause]

MICHAEL LEDERMAN, M.D.: Thank you, Jack, for that kind introduction. I'd also like to thank the meeting organizers for allowing me to present you a somewhat biased approach to answering a question that's really been a puzzle in HIV research for the past 26 years.

It's very clear that HIV replication drives progression of HIV infection towards immune deficiency, but the question is how that happens. Specifically, is viral replication sufficient to explain the CD4 T cell decline? Or, if not, what other factors, or factor, contribute?

Before I talk about that, if we're talking about a disorder that's characterized by progressive loss of CD4-

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positive T cells, I thought it'd be useful to define the three flavors that T cells come in. This is both for CD4 and CD8-positive T cells. These cells can be divided into populations phenotypically that are naïve, effector or central memory T-cell populations. Among these populations, naïve T cells have the broadest diversity. These are the cells that, in principle, represent the entire portfolio of immune responses or T-cell immune responses that a person could possibly have in response to an invading microbial pathogen. Naïve T cells have homing receptors that concentrate them in the lymph nodes, which is where they wait, pretty much resting, perhaps undergoing some rounds of homeostatic proliferation to maintain their numbers, but they're sitting there and their main job is to respond to new antigens that are presented to them by antigen-presenting cells so that they can mature into the effector cells. These effector cells are the cells that truly mediate defense against microbial pathogens. Effector cells, in contrast to naïve cells, have homing receptors that make them want to go to tissues. Why? That is because that's where the action is. That's where invading microbes generally are, that's where infections generally take place, and that's where the effector cells have to go to deal with them. They do so in a variety of ways. Their job is a protective job. They're there to protect us. They do so in part by elaborating

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cytokines, which are proteins that one cell makes in order to communicate with and activate another. These cells, especially those of the CD8 variety, have the capability of being cytotoxic, meaning that they can kill cells that are infected by these foreign microbial pathogens. Their T-cell receptor diversity reflects only the diversity of current antigens that are floating around. The reason that's the case is because we're too small, each of us is too small, to possibly contain within our bodies a sufficient number of all the kinds of different lymphocytes that we need to protect us from all the infections that we could possibly need. That means that our immune response needs to be flexible, needs to be able to expand when needed and it needs to be able to contract when needed. As a result, effector T cells numbers contract and diminish dramatically when the microbial process and the microbial antigen have been cleared.

Now, what is it that allows the effector cells to come back when they see a new antigen, when they see the antigen that they have seen once in the past? That is a central memory T cell. Central memory T cells, like naïve T cells, have homing receptors that focus them and concentrate them in the lymph nodes. That's where they live. And when they see an antigen that they have seen before, as a result of prior antigen exposure – because our T-cell receptor diversity

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reflects only the antigens that we've seen before – they're capable of maturing again, rapidly, into a broad number of effector T cells that are capable of mediating protection. Their job is primarily effector cell renewal.

The model that I'm going to propose to you today is that it is the activation and turnover of these central memory CD4 T cells that is central to the pathogenesis of CD4 T cell losses in chronic HIV infection.

We can learn a lot about HIV pathogenesis from studies done in non-human primates that are infected with a related simian immunodeficiency virus. Here are two different non-human primates, two different kinds of monkey that, when infected with the very same virus, have a very divergent outcome. On the one hand, we have the sooty mangabey, which is a naturally adapted host to SIV – it's an African monkey that, when it gets SIV, seems to tolerate it pretty well. It doesn't get sick. In contrast, we have an Asian monkey, the Rhesus macaque, which, when experimentally infected with the very same isolate, can often develop aggressive infection and a syndrome very much resembling AIDS in humans. So, how do these syndromes differ? Well, here's a Rhesus macaque on the left. Here is a sooty mangabey on the right. Both have high-level viremia, so it's not that the sooty mangabey controls viral replication. In fact, the magnitude of viremia in these

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animals is exceedingly high. But in contrast to the Rhesus that has circulating CD4 depletion, CD4 depletion is very rare in the sooty mangabey. They almost never get opportunistic infections. What distinguishes this pathogenic model from this non-pathogenic model could be the level of immune activation. These animals that tolerate, which have evolved over millennia, living with SIV, the ones that are still around have somewhat figured out a way maybe to ignore it and not get activated in the setting of chronic viral infection.

Every time I read these articles – and these are the two initial reports of AIDS from two different groups that appeared in *The New England Journal of Medicine*, I'm really stunned at how thoughtful and insightful these physicians and scientists were. They immediately recognized that something wasn't right in their patients. They immediately looked to sort of what it was and came to the conclusion, which still holds today, that there is profound depletion of CD4-positive T cells from the blood, CD8 T cells are relatively preserved and the function of the CD4 T cells that remain is impaired. Well, one thing that is often forgotten is that they also observed that the remaining T cells in circulation had high-level immune activation as recognized by recognized by reactivity with a monoclonal antibody called OKT10. We know call the antigen recognized by OKT10 CD38, an activation marker.

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It's hard to talk about immune activation without recognizing the vital work by the now late Janice Georgy [misspelled?], who, in the early 80s, was really persuaded that immune activation was driving CD4 T cell losses in persons with HIV infection and AIDS. In a number lovely studies, both in her own cohort at UCLA and also in collaboration with the Macs [misspelled?], she had recognized and demonstrated that immune activation, though correlated with the magnitude with viremia, was an independent predictor – and in some ways a better predictor – of disease progression risk, than was the magnitude of HIV viremia. Some other studies have confirmed this work and similar studies in the Amsterdam cohort have demonstrated that another activation marker, even among persons measured even before acquisition of HIV infection, that the magnitude of immune activation, as recognized by high levels of CD70 expression, predicted disease progression risk. So there is something about immune activation that is related to the risk of getting sick with HIV infection and AIDS.

What do we mean by immune activation? Activated cells express activation markers like CD38, for example, like H0 class II MHC, HLA-DR on T cells. Activated cells make more stuff. They're turned on and they do things. B cells make more immunoglobulins. T cells, natural killer cells, monocytes and other antigen-presenting cells make a whole variety of

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cytokines and chemokines. What cytokines are, again, are just proteins made by one cell as a means to talk to, communicate with and activate another cell at a bit of a distance, so they can do this without even touching cells. But, very importantly when we talk about immune activation, activated cells also may enter cell cycle with an intent – a wish – to divide. T cells do that very commonly when a T cell recognizes an antigen by binding to its T-cell receptor. T cells enter cell cycle to divide and their goal is to expand the immune response – make more baby cells, each one just like the mother cell, so that the immune response to that particular antigen is amplified. But T cells can also be induced to divide and enter cell cycle by what is called bystander mechanisms, that is, specifically or by example, by exposure to certain cytokines. So you don't have to be activated by an antigen through your T-cell receptor in order to enter cell cycle and try to divide.

So, how do we measure cell cycling and cell turnover? If we're thinking about sorting out how HIV causes disease and makes people sick and if we're losing CD4 T cells, it is plausible to at least propose that the loss of these cells is via activation and turnover. Well, we can measure cells within a cycle that are cells that want to divide in several ways. One way is by measuring cells that are expressing Ki67. Ki67 is an antigen, a nuclear antigen, which is expressed only by

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cells within cell cycle, cells in G1 and the DNA synthesis phase and in the G2 mitosis phase when they start actually dividing, but it's not expressed on cells that aren't thinking about entering cell cycle, cells in the G0 or resting phase. This antigen can be measured by flow cytometry. Another way is by feeding cells a thymidine analogue called bromodeoxyuridine or BRDU. BRDU looks like thymidine and is incorporated into the growing DNA strands of cells that are synthesizing DNA in the S phase of the cell cycle.

At the NIH, Joe Kovac [misspelled?] used BRDU labeling to actively demonstrate that there is high turnover of cells – CD4 cells, as well as CD8-positive T cells – in untreated HIV infection and when we treat people with antiretroviral drugs to limit viremia, this high turnover is attenuated dramatically. It's not just in the peripheral blood. I want you to also recognize and see that this was demonstrated as well in the lymph node, both before and after treatment.

So, a question that is really important now is which cells are turning over, which of the maturation phenotypes that we talked about in the T cells are turning over, and what is driving them into cell cycle? Why are they turning over? What's the mechanism by which they're being persuaded to enter cycle and turn over?

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Scott Sig [misspelled?] at our group looked at this in some work that was published two years ago and found that most all circulated [inaudible] cells, the BRDU-positive cells in peripheral cells, are what we call central memory cells. They're the vast majority of all these cells that are in cycle. Interestingly, although their frequency correlated very nicely with viremia, none of these cells were HIV reactive, so they weren't being driven by responses to antigen. Importantly, when we looked at the characteristics of those cells in a variety of different ways, they weren't behaving as if they were being persuaded to go into cell cycle through activation through the T-cell receptor, but rather they were being activated by what we call bystander mechanisms. Some central memory cells, as I mentioned before, home to the lymphoid tissues. Perhaps that's where bystander activation is taking place. If so, how would that be?

In contrast to the heart, the lymph node is not a piece of meat. It's an actual delicate organ where interesting things happen. [Laughter] There must be a couple of cardiologists in the room. The lymph node is where immunologic recognition takes place. This is where naïve T cells live. This is central memory T cells live. Naïve T cells must undergo homeostatic proliferation and expansion, usually largely bystander mechanisms, in order to sustain their

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numbers. This is where naïve T cells first encounter antigen and mature into effector cells or central memory cells and this is where central memory cells also see their antigen that allow them to expand and make more effector cells that can go out into the peripheral tissue and protect us from getting sick.

But, in HIV, the story is a little different. A number of groups have demonstrated – I've shown them not very well over here. I'm sorry about the way that slide came out. In HIV disease, the lymph node is really enriched with a large number of effector T cells. So what are the potential consequences of this? Remember, these are the cells that are like bags of cytokines. They make cytokines all the time and they have cytotoxic molecules that help them kill target cells. Angelippe Encarto [misspelled?] addressed this question by looking at lymph nodes from 12 HIV-positive patients and 10 HIV-negative controls and she cut them up into little sort of bits and put them in histoculture inside tissue culture wells so that they were living together with their friends. They weren't all suspended. They were just in little bits of lymph node. And then she evaluated the amount of cytokine that was elaborated by these unstimulated lymph node histocultures after two weeks of culture. What is shown are the data here that show the ratio of the cytokine in lymph nodes of the HIV-positives over those in the lymph nodes of the HIV-negatives.

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Every cytokine that is above the line is a cytokine in which the average level is much higher in the HIV-positive node. Every bar that's below the line represents a cytokine where the cytokine levels were lower in the HIV-positive node than the HIV-negative node. You can see that there's a fairly robust distribution of a variety of different cytokines whose expression is much higher in the HIV-positive node. I want to draw your attention two special cytokines, interleukin-2 and interleukin-15. These are both what are called common gamma chain receptor cytokines and each of these cytokines is capable of bystander activation and driving T cells into cycle. The question is whether these cytokines are driving bystander activation and turnover of central memory T cells in the HIV-positive lymph node. So, that's question one.

A little change in gears right now and I'm going to address another possible mechanism, whereby HIV infection can result in broad systemic immune activation. This was a model that was proposed about a year-and-a-half ago by Jason Brenchley and Danny Douek in an opinion piece in *Nature Immunology*, where recognizing that acute HIV infection produces dramatic and what they call catastrophic destruction of the CD4-positive T-cell population in the gut-associated lymphoid tissue. They were wondering whether or not that effect, that acute early effect, resulted in a loss of the normal barrier

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that keeps microbial products within the gut. They proposed that in HIV infection perhaps it was translocation of microbial pieces, pieces of bacteria that got into the systemic circulation and ultimately resulted in broad systemic immune activation.

A paper that came out this winter demonstrated that in fact this was the case. In persons with chronic infection and AIDS, the levels of lipopolysaccharide, which is a major constituent of the cell wall of gram-negative bacteria were substantially elevated when compared to those persons who were uninfected, as well as compared to people with acute and early infection. I won't go into the details of that issue, but perhaps Jason Brenchley will do so in his presentation a little later in the course of this meeting.

I summarized the results of their paper here in that levels of plasma LPS correlated with markers of immune activation in persons with HIV infection. They also correlated inversely with the magnitude of CD4 T cell restoration after heart [misspelled?], suggesting that there was some relationship between levels of microbial translocation and the ability to sustain CD4 T cell homeostasis in chronic HIV infection. Importantly, in these non-human primate models, plasma LPS levels were increased in the pathogenic Rhesus model, which is the one where there is high level of immune

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activation and CD4 depletion, but not in the non-pathogenic sooty mangabey model of SIV infection. They concluded that increased levels of LPS reflected a diminished gut barrier not just to LPS, but to a whole variety of microbial elements that were ordinarily sustained and retained within the microbe-laden gut lumen. In fact, that seems to be the case.

In some additional work – and these are slides provided to be by Danny Douek and Jason Brechley – there were high levels of bacterial peptidoglycan in the plasmas of HIV-positives and not in the plasmas of HIV-negatives, and they also found high levels of bacterial DNAs in the plasmas of HIV-positives, but not in those of HIV-negatives. So there is clear evidence that in chronic HIV infection, microbial products seem to get in systemically.

So, how do they drive immune activation? Well, probably this is how. I talked before about the adaptive immune response and how, in order to generate an adaptive immune response, you needed to amplify the frequencies of cells that responded specifically to a peptide derived from the microbe of interest. Well, that doesn't get you through the night. It takes a while for that to happen. But there's another way of protecting ourselves against microbes. One way to do that is if you divided the entire microbial world into 10 different patterns, 10 different structures that were shared –

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by at least some microbe had at least one of those patterns. If you developed a receptor that was capable of recognizing each of those 10 patterns, it might be a way, if you distributed those receptors on epithelial cells, in the gut, in the respiratory tract, on the skin and on professional antigen presenting cells such as macrophages and dendritic cells that frequently encounter microbes, you might be able to – if you distribute them properly – recognize any microbe that you came into contact with and generate some sort of response, some sort of recognition that they're there. That's what [inaudible]-receptors do. [Inaudible]-like receptors can be found on the cell surface and they can also be found within endosomes and they recognize a variety of microbial products, often glycolipids, sometimes proteins like flagellin that are shared by a variety of bacteria, as well as microbial genetic sequences, double-stranded RNAs, single-stranded RNAs, as well as unmethylated CPG DNAs that come from bacteria.

We've got these [inaudible]-like receptors. In our group, Anaka Luciano [misspelled?] and Nick Fundeberg [misspelled?] asked the question as to whether or not any one of these [inaudible]-like receptor ligands derived from these microbes could activate T cells. The answer is that they could.

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These are summary data from the means of 20 experiments where he found that if he took peripheral blood mononuclear cells and exposed them to a variety of different microbial TLR agonists, CD4 T cells that were activated in this way entered cell cycle, as reflected by expression of Ki67, which is up there. CD8 T cells, on the other hand, didn't enter cell cycle nearly as much, but they were activated to express the C-type lectin CD69. I'll tell you a little bit more about what CD69 does in just a moment. If these CD4 cells are being activated by microbial elements to enter cell cycle, we need to know whether or not it's successful, whether they complete cell cycle and divide and make baby cells or whether or not they end up dying. One way to do that in the test tube is by labeling cells with a fluorescent dye. In these experiments, peripheral blood mononuclear cells are labeled with a dye called CFSE, which is a green fluorescent dye, and then cultured with activation stimuli for various period of time, from 3 to 7 days. And then at the end of the period, they're washed, they're stained for surface CD4 or CD8, and then they're run in a flow cytometer. In the flow cytometer, we can see that cells that divide successfully dilute the dye to their daughter cells so that each daughter cell has half as much dye as the mother cells does, and with a subsequent dilution or division, each of those daughter cells has one-quarter as much dye as did the

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original mother cell. We can see dilution of dye as one division, two cell divisions and, in fact, we can even discern as many as five or six cell divisions using this technique. At the same time, if we want to ask whether any of these cells are dyeing because they're not completing cell cycle and they're activated, we can examine their binding of annexin 5, which binds to the surface of cells via apoptosis. In fact, that is what seems to be happening when cells are stimulated by [inaudible]-like receptor ligands. Here's a flow cytogram showing CFSE dilution on the X axis, annexin 5 binding on the Y axis, and here are cells incubated with medium alone, [inaudible] here on CD4-positive T cells. They haven't diluted much dye and there's not a lot of cell death. In contrast, when we stimulate cells through their T cell receptor, the way antigens would stimulate cells, we get pretty reasonable dilution of dye and a little bit of cell death, but look what happens when we stimulate with flagellin A, which is a TLR 5 agonist. Even though these cells move into cycle, we showed you that many of them become Ki67-positive, very few of them actually dilute die, meaning that they've completed division. But about 17-percent of them in this experiment bound annexin 5, indicating that they were going to die. When we looked at a whole variety of [inaudible]-like receptor ligands, focused on the CD4 T cells in this panel, we saw that poly IC, LPS,

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flagellin A, flagellin B and imiquimod all were capable of driving these cells into programmed cell death. You can see details of this on Nick Fundeberg's poster on Wednesday.

It looks as though TLR ligands induce bystander T cell activation. It's not mediated through the T cell receptor. The way they activate these T cells are through multiple mechanisms – memory and effector CD8 cells are activated to express CD69 and that makes them sticky, because when T cells are activate, when CD8 T cells are activated to express CD69, this blocks expression of a surface receptor called S1P1 that is needed to allow activated T cells to leave the lymphoid tissues.

But look what happens when we stimulate with flagellin A which is a TLR 5 [misspelled?] agonist. We get limited, even though these cells move into cycle. We showed you that they all, or many of them become KI67 [misspelled?] positive. Very few of them actually dilute die, meaning that they've completed division. But about 17 percent of them in this experiment bound to nexin 5 [misspelled?], indicating that they were going to die.

When we looked a whole variety of tolicreceptor [misspelled?] ligands focused on the CD4 T cells in this panel, we saw that poly IC, LPS, flagellin A, flagellin B, and imiquimod, all were capable of driving these cells into

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programmed cell death. And you can see details of this on Nick Funderburg's poster on Wednesday.

So, it looks as though TLR ligens induce bistandard T cell activation. It's not mediated through the T cell receptor. And the way they activate these T cells are through multiple mechanisms. Memory and affecter CD8 cells are activated as express CD69, and that makes them sticky. Because when T cells are activated, when CD8 T cells are activated, to express CD69, this blocks expression of a surface receptor called S1P1 that is needed to allow activated T cells to leave the lymphoid tissues. So they are stuck there. They're stuck in the swollen lymph node. Central memory CD4 T cells are activated by exposure to these tolicreceptor ligens to enter cell cycle and to die. To turn over.

And to demonstrate that this may have direct relevance to the direct role of HIV in terms of inducing immune activation, Bruce Walker's group just published in this month's issue of *Journal of Urology*, the observation that certain viral Ranks [misspelled?] that are enriched for poly-U [misspelled?] sequences are capable of expressing, inducing CD69 expression here on CD8 positive T cells as well as on CD8 negative T cells. And here our control RNA sequence had no such effect. So, HIV can activate tolicreceptors directly.

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So here's the model. The model is that in HIV infection we have activation of both the adaptive and innate immune system, and that's what drives HIV pathogenesis in the lymph node. First we have viral replication in the lymph node, and this is usually not the place where our microbes replicate. Because of this, we have the influx of HIV specific effector T cells that make a whole bunch of cytokines and make this environment very, very inflammatory. This inflammatory environment results in additional trapping of more effector cells of diverse specificity, so these are non-specifically activated and sequestered within the lymph node. And this cytokine environment drives central memory cells by common gamma chain cytokines into cell cycle and to death. Additionally, this chronic exposure to inflammatory cytokines in this very messy lymph node, results in the development of lymph node fibrosis as shown elegantly by Tim Schacter [misspelled?] and this lymph node fibrosis and this changing of the stroma of the lymph node results in an environment that is simply not amicable for naïve T cells to expand properly.

Finally, we have systemic exposure to these microbial products that get in from the damaged gut and they show up in these lymph nodes and activate toll receptors to additionally sequester more effector CD8 positive T cells and to drive more central memory CD4 T cells into cell cycle and death.

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To put another way, we have HIV replication that drives immune activation, directly and indirectly. It also produces damage to the gut reposita that results in translocation of a variety of microbial products that also enhance immune activation in the lymph node. As a result of this immune activation, HIV replication is enhanced, because an activated T cell is much more capable of supporting HIV replication than is a resting T cell, and because of this immune activation we're also driving progressive CD4 T cell losses that also fails to constrain viral replication.

So, 11 years ago, John Coffin [misspelled?] showed us a lovely model, a schema, of a train wreck in which the CD4 T cell count told you how far you were, how much time you had, or how far you were from the cliff, and the viral load told you how quickly you were going to get there. I'd like to propose a modification to this model, where still the CD4 T cell count is the distance from the cliff. And in this engine, the viral load is the fuel. Without fuel, you're not going to move. But the speed of the train depends on a variety of factors. One for example, could be, in this concede, could be the engine gear ratio, and in that regard, we're talking about host factors that I haven't even addressed, but there are a number of host factors that do contribute substantially to the pace of which HIV disease causes immune deficiency. And the speed of

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the train also depends on the fuel mix. And that is, can be defined as immune activation as driven by viremia and by other factors, such as for example, other microbial toll-like receptor ligands.

So, should we try to suppress immune activation? Should we interfere? Should we give them immunosuppressors, to people with chronic HIV infection in the HAART era? It's a tough question because now our drugs are better tolerated. They're less toxic. We have once a day, we have drugs that can be given once a day. And we also have inexpensive drugs that are available for the developing world. But we could, if we wanted to, to ask the question that perhaps we could enhance CD4 T cell restoration in those persons who have fairly modest increases after control of viremia with HAART [misspelled?]. We could try to enhance CD4 T cell restoration in persons with incomplete suppression of HIV replication because they have multi drug resistant virus. And interfering with the downstream mediators of pathogenesis could permit them to live a more immunologically competent life. One could even conceive of the possibility that administering suppressive agents could delay the initiation of HAART, but public health issues need to be addressed in this regard.

Many people think that immune activation and CD4 depletion are co-factors that contribute to the heightened

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appearance of non-AIDS complications of chronic HIV infection.
Could immune suppressors be of value in this setting?

And then finally, do we need to normalize CD4 T cell counts in treated HIV infection? I don't know if we do, but I just want to show you some data from our center that was put together by Benino [misspelled?] Rodriguez and Howard Myerson [misspelled?] where we looked at the frequency distribution of CD4 T cells in people with, who had been on heart for at least five years and whose last viral RNA was below the defined normal range. And in these experiments, 20 percent of these individuals, 20 percent individuals had a CD 4 T cell count that was below the normal limits in our population.

So, I'd like to thank the people who contributed to this work, specifically Scott Sig [misspelled?], my faculty colleagues, [inaudible] Scott Sig and Benino Rodriguez. My graduate student, Nick Funderburg. My [inaudible] Anka Luciano [misspelled?]. My collaborators at the VRC, Jason Benchler [misspelled?] and Danny Duak [misspelled?]. And my collaborators at NICHD, [inaudible] Margolis, Angelique Yonkato [misspelled?], and John [inaudible], and finally, I'd like to thank the BBC. This is a group of scientists who have been thinking about HIV pathogenesis for the past three years. We've been meeting in Cleveland at least twice a year to talk about this, and the discussion that we've had have really been

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central to molding my thoughts about this, and just to be clear, it's not that we don't have women in the group, but the three women who are part of the BBC are too gracious, too elegant, and probably too sober to be seen with us in public. So thank you. [Applause]

FRANK BOWDEN, M.D.: My name's Frank Bowden, and I'm from the Australian National University in Camborne. I'd like to introduce Dr. Brian Gazzard who will be talking about aging and AIDS. Professor Gazzard qualified from Cambridge University and received his M.D. from the same institution in 1982, and he's a fellow of the Royal College of Physicians. He's a consultant at the Chelsea Westminster Hospital, and he says that he saw his first AIDS patient in 1979, something which he tells me has more to do with the revelation of his age more than anything else. In 1991 he founded the Stevens [misspelled?] AIDS Trust and he's also the Founder and Chairperson of the British HIV Association. He was elected to Professor of HIV Medicine in 1997, and in 2002 he was awarded a prize for clinical leadership at the 20th anniversary celebration of the Terrence Feagans [misspelled?] Trust. He's also received an Outstanding Achiever for Health Award from the U.K. government, so it gives me great pleasure to introduce Brian Gazzard. [Applause]

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BRIAN GAZZARD, M.A., M.D., F.R.C.P.: Good morning.

Thank you for inviting me here. The main purpose of me coming was to buy a new jacket, which [inaudible] I'll never have the nerve to wear again. Many of us in the audience are becoming increasingly concerned with aging. For some of us, that has brought an increasing degree of sobriety, elegance, and intellectual merit, as compared with the picture shown here. Before I begin my talk I think it's terribly important to recognize that we are talking about aging in a developed world. If you are in Malawi and you are 55 and you're diagnosed as HIV positive, your prognosis is zero ten years later. So let's bear that in mind. One of the many questions I'm often asked legally is will this guy who is now HIV positive now live a normal lifespan? And it's one of the few advantages to being very old that I can remember the time when I discussed with my patients dying with dignity and that we were try to ensure that they lived as long as they could by treating opportunistic infections. And now of course we can talk about decades of extra life with antiretroviral therapy. But is this back to normal? Well you can see here from the art collaboration mainly North American and Canada that the life expectancy of a 20 year old is improving year by year, but that it's still short of that of the general population. And so even in 2005 there's a very considerable shortening of life with a lot of

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time lost. And the purpose of this talk is really to discuss with you why that might be and how that is very much related to diseases of aging that are commoner in HIV infection, and have a worse prognosis. Clearly this sort of data has to be taken with a pinch of salt. HIV even in the developed world is a disease of the dispossessed and these people have shorter life spans. And indeed this is data where the life expectancy of the intravenous drug user has been removed. Clearly with our improved treatment, there is no doubt that the prevalence of HIV is increasing in older age groups. I could have chosen any number of cohorts for this, but this is the U.K., where now a third of all adults are 55 years or over who are HIV positive. A really quite staggering statistic. Many older people are anxious about whether sex will continue into old age, and I would just like to say that yes indeed it does. Here is the Cascade analysis of seral conversion of HIV positivity in older people. As you can see here, 2,000 people in the Cascade analysis first were diagnosed with, first correlate HIV in the over 50s, so that's good news for some of us. Obviously the question that I'm being asked to address is a complex one because it's an interrelationship between the aging process between HIV and of course the potential affects of heart. This is one of my very early patients who edited a magazine called *She*. It was a magazine entirely for women only on the top

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shelf, and he was the editor of this magazine and when he was short of a centerfold, he felt himself to be good looking enough to appear on a fairly regular basis. But then he got HIV and within six months, he had aged in a tremendous way, and we used to say that many of the effects of HIV were strongly related to aging. I've obviously had to do quite a lot of reading about aging, and there's an enormous literature. I think it's rather schizophrenic. It's divided into two bits. Clearly many AIDS researchers feel very guilty about even discussing whether aging is something you should research into and they've come to the regrettable conclusion that the lifespan of man is more or less fixed where we are now, and it's fixed really for two reasons. One, there's no Darwinian reason, Professor Cooper, for survival beyond the age of reproduction, and secondly, the third law of thermodynamics. The second law, that is, as opposed to the first law, indicate that we'll all be dust in due course. Nevertheless, large numbers of researchers are interested in the process of aging and the elixir of life. And it is quite interesting that HIV per se will also affect many of these molecular mechanisms. So, therefore senescence is the invective capacity of cells to suddenly die after many divisions related to [inaudible] shortening as a feature of HIV, as we've heard very eloquently in the previous lecture. Apoptosis is an important feature

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that HIV can produce. And there is a constant issue about reactive intermediates and mitochondrial dysfunction. All important aspects of aging, so HIV may accelerate aging per se. Certainly the best evidence for that probably comes from the immune characteristics on old age, which are very similar. You see this whole list of things that [inaudible] is talking about which are all things actually which old people have. And particularly these late differentiated CD4 CD8 cells accumulate and there's a paper earlier this year that showed the risk of you dying as an old man if you have a collection of these cells and you CMV [misspelled?] positive was actually enormous. So these characteristics of aging and the immune system go together, and interestingly enough not only is it the cells, but it's not surprisingly also their function. There's a very good study where people who were HIV suppressed with CD4 counts greater than 200 were given Hepatitis A vaccine, and the immune responses as you can see were very closely correlated with age. Here Professor Cooper, the chances of you getting a response are very low.

It's also true that IL2 [misspelled?] doesn't work very well in the elderly. So this is from the Esprit group. An excellent slide. I've got to say that, otherwise Ians [misspelled?] will hit me afterwards, but an excellent slide from *HIV Medicine* showing that if you are old, your response to

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IL2 is not very good. So, we have a poor immune response in older people. What about the response to heart measured by the CD4 count, by appearance, and by AIDS and non-AIDS mortality. Here we have a slide taken from JID [misspelled?] where actually it was, it wasn't age [inaudible], it was age [inaudible], for simplicity. That the younger people had a much greater CD4 count response than the older people. Like everything in this world of HIV, you can find ten papers to show something different, but most of the papers tend to show that the immune response to heart is reduced in older people, presumably because of a lack of thymic output. Nevertheless, there are some good things about old age. And one of them is we adhere better to therapies, and this is a series of papers taken from the CPCRA analyses of adherence. Overall adherence is better if you are over 50, particularly better adherence of greater than 95 percent. And perhaps not surprising therefore, in the CPCRA studies, this led to a greater range of undetectability at less than 50 [inaudible] for those who were older.

Does that result in improved survival? Well, now we know here this is a slide, pre-AIDS where older patients, in this case, greater than 55, survived significantly worse than younger patients without treatment. However, with treatment, now there is no obvious treatment between older and younger

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patients in this analysis which is quite small. It has to be born in mind that many cohort studies actually in contrast do suggest that actually older people survive less well. And the rest of this talk is around why that might be. And what chronic diseases are associated with both aging and with HIV. There are a whole range of social diseases, Professor Cooper, such as social isolation, alcoholism, and dementia that are commoner in HIV, but we haven't got time to discuss these this morning. They would make a talk on their own.

But most chronic diseases that we recognize which are diseases are aging are commoner in HIV positive individuals, and in multi, varied analysis, age remains a factor for them occurring, so chronic liver failure, liver disease, big increase in mortality from liver disease in older people, and obviously bone mineral density, which doesn't usually kill you, but nevertheless osteoporosis is very much associated with AIDS. And I'm going to spend most of the rest of the talk on what I call the geriatric giants. Those things that will kill most of us in due course.

But first of all, just to show you. This slide again from the excellent Urocita [misspelled?] group showing this is for ten years, increments of age, a very major increase in risk of chronic renal disease and chronic renal failure. So there's a changing perception of HIV infection that as we get older

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many of the diseases of old age will kill us, and they will more likely kill us if we're HIV positive than if we're HIV negative.

So moving on to atheroma, just of course the most important thing that will determine whether we get cardiovascular disease is our genetic makeup. The second most important thing is smoking. And there's nothing like an ex-smoker to be [inaudible], and so I have not smoked since January the 1st, and I think it's a complete disgrace that some people will be outside having a quiet fag hoping that nobody will be watching them, and more important, that I think that much of this conference will be discussing very minor differences in which boosted PI to use instead of spending more time discussing why smoking cessation is an [inaudible] part of our clinical program.

Nevertheless, in terms of drugs, this is a very, again, a very large and very influential trial, the DAD study. And this is the publication in *New England Journal of Medicine* earlier this year showing that when you adjust for NNRTI exposure, there is per year an incremental increased risk of developing cardiovascular disease related to drugs. And this of course is a cohort study and in the same article there was a very learned review of all the problems associated with the cohort study including channeling and ascertainment bias, which

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of course the authors were well aware of and they've done their best to correct.

In this study, of course, age, the older you are the more likely you are to get myocardial infarction. That's not surprising. Men get it worse as well. Smokers have a terrible time. And it's the genetics also are bad for you. One of the interesting things about the DAD study, I think is that the relative risk is going down with each calendar year, so the longer you've been exposed to these drugs, actually the relative risk seems to be diminishing that you will get cardiovascular disease. And of course, the DAD group believed that this is because, probably rightly, we are using drugs more sensibly, and we're giving more people statins. But it does give one pause for thought that it may not be as simple as an increased cardiovascular risk related to drugs.

The Smart study, of course, had many surprises in store for us. But one of the biggest was I think this slide which shows remember, the drug conservation arm is really the same as people who are having an STI, and this is the viral suppression arm. A very clear difference emerging quite early on in terms of numbers of years of the cardiovascular risks and events if you stop therapy. Really the reverse of what most of us intuitively thought would happen, but an increased cardiovascular risk. Justifying what of course I've been doing

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for many years, which is taking Azithromycin on a weekly basis as a prophylactic for my cardiovascular disease, not the risk of other sexually transmitted infections. [Laughter] But this increased risk does make us go back to some of the original work done by [inaudible] Bizetti [misspelled?] in the *New England Journal of Medicine* here showing an increased uptake of antiretroviral treatments, a reduction in mortality, but this considerable reduction in cardiovascular admission rate halved over a ten year period that he was looking and everybody said, oh that's because they haven't been on drugs for long, but I think he may have been right all along. In other words, HIV itself is associated with a very big increase in cardiovascular risk. That is reduced enormously by antiretroviral drugs, but not actually necessarily back to completely normal. Very different idea to those that we had before.

Don't worry I'm not going to take you through this slide. This slide, Peter Rice did an unbelievably elegant talk recently where each of one of these individual mechanisms was talked about in great detail and I came away feeling very much better about myself and then tried to write it down ten minutes later and couldn't remember a word of it. And I'm a great believer in biological reductionism. I think that the explanations of true things are very simple. So I personally believe that in terms of the etiology of atheroma, we're

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missing a trick. HIV may be telling us something unbelievably important about the genesis of atheroma, which when we understand that will actually be simple. As a guessing man, I think it's actually all something to do with the surface markers and [inaudible] and all that jazz here that's allowing stuff into the cell wall. Back to immunology yet again.

We were amongst the first to show, this is a slide from our unit, just to show that because we've got a big cohort we can do a bit of work showing early on that a number of non-AIDS related cancers are increased in incidence, so seminoma, anal cancer, head and neck cancer, and lung cancer. We were desperate for the seminoma data to be significantly different, so we had to count one person twice, but he did have a seminoma in both testicles. Fortunately for us, this work has been confirmed in much bigger studies. And of course, most interestingly that HIV also causes, is associated with an increased age specific risk of lung cancer. And in the DAD study, the DAD study showed very nicely that fatal malignancies were now commoner of non-AIDS defining fatal malignancies than they were of AIDS related. So a large number of people who are HIV positive are dying prematurely of cancers and they're not necessarily classic cancers that we associate with AIDS. These cancers are commoner the lower the CD4 count, but also commoner the older you are.

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Now how does cancer come about because of HIV infection? Well clearly it may be because the people who are at risk of HIV infection are also at risk of acquiring oncogenic viruses, or it may be because there's a loss of immunosurveillance allowing this oncogenic viruses to proliferate. It would also be nice if HIV were capable of promoting cancerous, well not nice, it would be interesting, if HIV were capable of promoting cancer itself. In an unbelievably elegant paper in *Cell* which I would recommend you all to read, absolutely superb example of biological reductionism where there is a review of how all cells that become cancerous do so showing very simplistically in ways which even I can understand all these six mechanisms which probably apply to all cancers, and the really interesting thing of course is that HIV can interfere with all those mechanisms. So both signals, retinoblaster [misspelled?] protein, are very much interfered with by HIV, apoptosis as we've discussed, telomerase function as we've discussed, angiogenesis and veg [misspelled?], et cetera, so it may be that some of these cancers are actually being stimulated by HIV itself, rather than loss of immunosurveillance.

In last week's *Lancet* there were a series of papers which will change the aspect of HIV in medicine, and I had to make these slides as a result of reading the *Lancet* last week.

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Because what the *Lancet* did was what this study has done is a very good meta analysis of putting all the cancer cohorts together. As you know they were done very much in Australia in [inaudible], and John Colder [misspelled?], et cetera, and all those big cohorts have been together to provide a meta analysis and the interesting thing that they've done is also looked at transplant increased cancer risks as well. And if the two risks are both increased, you would suppose that it's more likely to be a problem about immunity in tumor surveillance rather than an intrinsic property of HIV that we get more cancers. So here we have a large number of EBV related cancers, the composita-sarcoma related cancers, the cancers related to liver disease, and indeed cancers related perhaps to [inaudible], and the stomach, both being raised in both HIV and transplantation. Here we have a whole range of cancers increased risk with HPV related cancers, head and neck cancer, et cetera, et cetera, down this list here. Again, transplantation and HIV both increasing the risk. Whereas with most epithelial cancers, there is no excess risk of cancer with HIV. The one exception being cancers of the bronchus and lung, which are increased in again both transplantation and HIV infection. And some interesting cancers where you wouldn't necessarily suspect them, oncogenic virus, melanoma, leukemia, multiple myeloma, all increased risk in both HIV and

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transplantation. And just a very small number of cancers where there is a risk in transplantation, perhaps the specific reasons with regard to [inaudible] and with the thyroid whereas it's true of transplantation but not HIV. And a couple of cancers where it's only true of HIV and not transplantation. So, I think some very definitive evidence about what cancers we're going to expect to be increased in our patient population and showing that this is really related to [inaudible] surveillance.

Finally, what about HIV and dementia? I've sat at a lot of lectures given by eminent people about HIV and dementia, and I keep thinking well I don't see that in my practice, but I am told it's a very subtle change. That HIV related dementia is changing. That there is certainly evidence that glycosis may continue in the brain despite apparently good HIV control, and this is said to correlate with proviral DNA. That itself may increase the risk of dementia, and there are theories to suggest that HIV itself may encourage Alzheimer's disease. So what is different about ADC now? Well apparently it's more cortical. You can't remember things as a presentation rather than you're ataxic with subcortical presentations of before. The temporal lobe is more likely to be involved than the basal ganglia by PET scanning and the old-fashioned strong correlations between the [inaudible] and the CSF, and the beta

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microglobulin are breaking down that people with age dementia may not have those changes. What about Alzheimer's disease? Well, in HIV dementia, there is beta amyloid deposition within the cells, shown there. There's also an extra amyloid plugs. There is less beta amyloid in the CSF, and there's enzyme which is supposed to break down the amyloid plugs is inhibited by [inaudible]. There's also increased expression of alpha protein A4, polymorphism. So there may be a whole new epidemic of dementia in store for us. But I'm hoping not.

I want to end this with two exhortations. One for the young in the audience. There is plenty of research still to be done in HIV. It's still a very exciting area, and the area of aging and neoplasia and those interactions are very, very important. Please make it simple. I'm a great believer that people who get the Nobel Prize have simple answers to complicated problems. Not complicated answers that nobody understands. For those of us who are growing old, I leave you with a 1631 quotation from John Donne, from his Tenth Sonnet. And just to translate it for you, because it's Elizabethan English, Professor Cooper, what it's really saying, what it's really saying is enjoy your life and have a good life and do good things with your life. Rather than be terrified of death right from life's beginning. You'll remember that John Donne was a very famous clergyman. But he was I'm glad to say like

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St. Augustine, perhaps the most profound experiment of
Christianity, who said, Lord make me good, but not just yet.
And I'd like just to introduce you to my one attempt at
immortality, who was born eight weeks ago, and both mother and
child are doing well, but husband is exhausted.

[Applause]

[END RECORDING]