



The AIDS 2008 Impact Report Evidence to Action

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Basic, Clinical and Biomedical Prevention Research

BASIC, CLINICAL AND PREVENTION RESEARCH

Basic Science

HIV has become a chronic, manageable disease for most patients in high-income countries, who can expect to live near-normal lifespans at current standards of care. Two major journal reports confirming this conclusion were released on the eve of the conference and brought a new focus to conference presentations on the basic biology behind the HIV-human host interaction.^{1,2}

Residual Viremia and the Limits of HIV Disease Management

Several presentations at AIDS 2008 examined the limits of medical management of HIV. The virus can be reduced to levels undetectable by standard assays, yet a small residual amount of virus remains, on the order of 1 copy of HIV RNA per millilitre of plasma. The source of this residual viremia is still the subject of debate, but its consequence is certain. Patients who stop antiretroviral therapy (ART), even after many years, usually see their viral loads rebound to pre-treatment levels within a matter of weeks. Absent viral eradication, ART is for life. The world is therefore faced with the need to administer decades of antiretroviral agents to 30 or 40 million people, with all the expense and toxicity management issues that come with such a massive undertaking.

Robert Siliciano summarized a decade's worth of research in his presentation on the origin of residual viremia.³ Siliciano's own observations have led him to infer that there is essentially no ongoing viral replication during successful ART. Instead, residual viremia comes from cells containing latent HIV DNA in their genomes. HIV becomes activated along with the cells' own genes during the immune response to disease.

There is no evolution in this latent population and thus no emergence of drug resistance. ART can control the residual infection indefinitely but it cannot eradicate it. More frustrating yet, the residual viremia in about half of all virologically suppressed patients seems cloned from a handful of isolates. Siliciano argues that on a few occasions, HIV becomes integrated into progenitor cells that faithfully copy the HIV genes as they divide and differentiate into mature immune cells such as monocytes and lymphocytes. Viral production begins only when these mature cells become activated.

In this context, the possibility of therapeutically eliminating all latent HIV or removing HIV that silently replicates along with the human genome in progenitor cell lines is remote. In a presentation, Anthony Fauci suggested a form of "immunotherapy" – in addition to early treatment and treatment intensification – as one strategy for gradually

eliminating the latent reservoir.⁴ While protected by the most potent ART, anti-HIV immune responses could be preserved and ultimately enhanced. Eventually, they might be strong enough, and residual HIV low enough, to allow for drug discontinuation without viral rebound.

The first step toward developing a therapeutic strategy for controlling latent HIV will be to understand more precisely how HIV proviral DNA integrates into human chromosomal DNA and the factors inducing latency. Kadreppa Sreenath presented data supporting suppression of transcription by SMAR1, a component of the cellular nuclear protein matrix; SMAR1 maintains the genes' physical structure as well as helping to regulate their activity.⁵ SMAR1, induced in response to HIV infection, forms a repressor complex with two other proteins that bind to the long terminal repeat region at the terminus of the HIV genome. HIV tat, together with the cells' own activation factor NF- κ B, displaces this complex and triggers viral replication. This model yields hints of a therapeutic strategy, involving either SMAR1 promotion or tat inhibition, but this concept is still far from a concrete therapeutic application.

The Challenging Speed of Acute Infection

The conference yielded multiple presentations of how rapidly HIV takes over during acute infection. Eric Hunter and Debrah Boeras showed that new sexually acquired HIV is usually very genetically homogenous.^{6,7} It arises from a minor variant present in the donor's body. Presumably such HIV has special, still undefined characteristics that make it more fit for transmission.

Once in contact with a new host, HIV moves very quickly. Yonatan Ganor described the results from his group's explant model of human foreskin.⁸ Cell-associated HIV was efficiently transmitted in this model. The Langerhans cells on the inner foreskin became infected with HIV and transferred the virus to the CD4+ T-cells in the dermis within one hour of initial contact. In contrast, transport from the outer foreskin was 10 times less efficient. Cells in the outer foreskin's keratinized layer could become infected but that layer kept the infection from spreading inward. Also, the Langerhans cells in this layer degraded HIV when they captured it rather than transporting it live to the virus's primary target.

The role of mucosal dendritic cells, of which Langerhans cells form a subset, in facilitating HIV infection has been known for some time (see Figure 4). Dendritic cells contain surface receptors containing C-lectin, to which HIV physically adheres.⁹ DC-SIGN is the most widely recognized of these receptors, but there are a number of others.

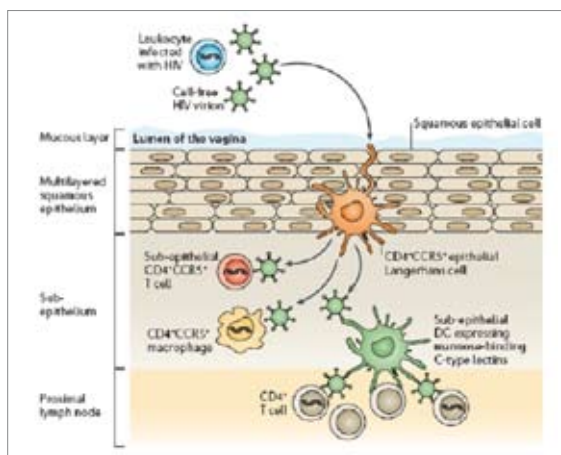


Fig 4. Cells Playing a Role in Genital HIV Transmission

Source: Vanham, G. *Future promising microbicidal products: What to learn from the in vitro work (THSY0601)*, from Lederman, M Offord, R and Hartly O. *Microbicides and other topical strategies to prevent vaginal transmission of HIV*. *Nature Reviews Immunology* 6, 371-382 (1 May 2006).

Dendritic cells' normal function is to present foreign antigen to the CD4+ T-cells, which then stimulate an immune response. The dendritic cell first internalizes the C-lectin receptor-HIV complex in an endosome. Endosomes normally break up foreign bodies for antigen presentation. Whether particular dendritic cell subsets actually degrade or protect HIV depends on the structure of their C-lectin receptors. This observation may help explain HIV's different outcome on the inner and outer foreskin – and hence the protective effect of circumcision.¹⁰

Tove Kaldensjö reported on four different dendritic cell subsets present on the female ectocervix.¹¹ Comparing HIV-negative women with high and low risk for HIV exposure, Kaldensjö's team found that the women with higher risk sexual behaviour had more ectocervical dendritic cells with C-lectin receptors capable of transporting HIV to lymphoid tissue.

Damage occurs very quickly once HIV starts infecting CD4+ T-cells. Fauci noted that HIV establishes a latent HIV reservoir in the first week after transmission. In addition, gastrointestinal effector CD4+ T-cells are virtually eliminated during the first few weeks.^{12,13} According to a recent report by Fauci's group, CD4+ cell counts in gut lymphoid tissue remain depressed even after 10 years of suppressive ART, and this tissue represents the location of most of the latent viral reservoir.¹⁴

Understanding Innate Immunity and the Role of Toll-Like Receptors

Halting HIV's rapid progress during primary infection is of prime importance. AIDS 2008 marked a new interest in innate immunity, which is the first line of defence against HIV. The initial inflammatory response arises from a variety of

non-specific, T-cell independent immune responses that recognize invasion by some sort of foreign material. HIV's encounter with innate immunity starts with the C-lectin receptors on mucosal dendritic cells. Though mostly ignored until recently, innate immunity remains a major factor throughout the HIV lifecycle.

Much of the new focus on innate immunity concerns toll-like receptors (TLRs). TLRs are an ancient family of cell-surface and internal receptors. They recognize molecules that are common to many pathogens but foreign to host cells. Present on human immune cells, including macrophages and lymphocytes, each receptor in the family specializes in recognizing a certain type of molecule – for example, bacterial glycolipids or lipoproteins and viral DNA or RNA. Once excited, TLRs start a signal cascade that results in cell activation and the release of inflammatory cytokines.

Research into the relationship between TLRs and HIV has accelerated dramatically over the past five years. The AIDS 2008 Scientific Programme included several inconsistent, and even conflicting, reports on strategies to employ TLRs therapeutically.

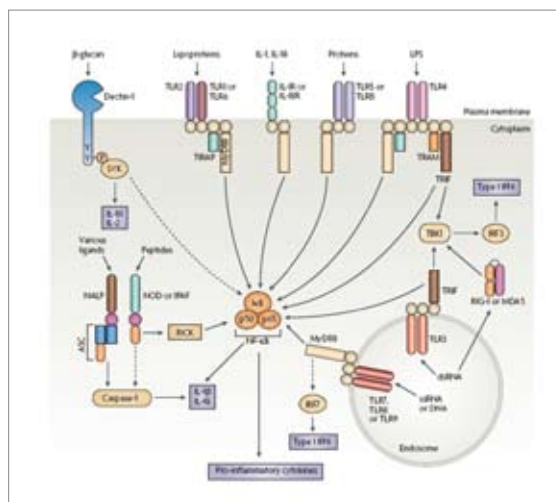


Fig 5. The Toll-like Receptors in and on Cells Recognize Microbial Patterns and Trigger Immune Responses

Fig 5. Source: Pimenta-Inada, H et al. *The Toll-like receptor 2 ligand Zymosan inhibits HIV-1 replication in human primary cells (MOAA0105)*, from Trinchieri G., Sher. A., *Nature Reviews Immunology* 2007 Mar;7(3):179-90).

Dumith Bou-Habib reported on zymosan, a common fungal polysaccharide that binds to TLR2. Zymosan inhibits HIV infection in macrophages, apparently at the cell entry stage (Figure 5).¹⁵ A synthetic compound, Pam3Cys has similar properties. However, Sandra Thibault reported that Pam3Cys and other compounds binding TLR2 and TLR5 on CD4+ T-cells actually increase cellular HIV integration and

production, a result that conflicts with Bou-Habib's findings.¹⁶ Terrance Brann's also presented findings suggesting the HIV suppressive effects of TLRs. His experiments were with a pair of TLR4 ligands produced by human neutrophils.¹⁷ These molecules reduced R5-tropic HIV replication in macrophage cultures but did not affect X4-tropic HIV in CD4+ T-cells. In other research, Leonid Margolis discussed ways in which viral co-infections such as HCV can up- and down-modulate HIV, probably by interacting with various TLRs.¹⁸

The inconsistencies in the studies presented require further investigation. One explanation may be subtle ways in which the TLR-signalled response directs chemokine and cytokine release. The zymosan report, for example found that macrophages respond to TLR2 stimulation by releasing beta-chemokines, the chemotactic signalling molecules that fit into and block the CCR5 receptor utilized by R5-tropic HIV when entering new cells. T-cells respond to TLR2 by producing NF- κ B, as do macrophages, but without the beta-chemokines.

The importance of the overall cell-signalling milieu was further stressed in a report published just after the conference. It described the HIV suppressive effect of a mutation in TLR8.¹⁹ The study, which included 782 HIV+ patients, observed that those with only the mutant (A1G) gene exhibited a mean CD4 decline that was 3.5-fold slower than HIV+ patients with normal TLR8 (75% of the total study population).

When stimulated, the mutant TLR8 triggers relatively lower levels of NF- κ B and IL-10 and relatively higher levels of tumour necrosis factor alpha (TNF- α) as compared with normal TLR8. All three are known to promote HIV replication, but TLR8 stimulation and TNF- α also activate protective CD8+ cytotoxic lymphocytes and natural killer (NK) cells.²⁰

NK cells are a type of white blood cell that non-specifically kills virus-infected cells. At AIDS 2008, Samuel Nuvor and colleagues argued that down-regulation of NK cells is a critical difference between HIV-1 infection and HIV-2, which progresses more slowly.²¹ Restoring NK cell activity via TLR8 or otherwise might be an important component in therapeutically or prophylactically creating an effective immune response against HIV.

Harnessing the Immune Response

Stimulating the immune system to better fight HIV is a complicated issue. Chronic immune system activation without achieving effective HIV control may be a major contributor to HIV-associated T-cell loss.²² Immune control and regeneration processes become exhausted or dysfunctional. They fail to replace cells lost to HIV or even cause more cells to die via a form of cell suicide known as apoptosis. A number of the factors contributing to immune decline were described at the conference. These include loss of proliferative capacity

and response to antigen presentation in HIV-specific CD8+ cytotoxic lymphocytes.^{23,24}

Notably, a post-AIDS 2008 report described increased cellular TLR levels and heightened responsiveness to TLR signalling in persons with HIV.²⁵ This report implicates TLRs in immune dysfunction during untreated HIV infection rather than as a source of protection.

Many of the conference presenters nonetheless suggested that their research findings will eventually help to identify ways to restore the immune response and devise new means for controlling HIV. The relevance of these results is not yet clear given the high degree of HIV control achieved by direct antiretroviral therapy. Suppressing HIV will by itself eliminate much of the chronic inflammation and allow immune recovery. The total CD4+ T-cell count does not seem to ever return to pre-HIV levels, however, and subtle defects in immune subpopulations remain.²⁶

An obvious next step will be to better delineate what constitutes effective anti-HIV immunity. Answering that question is complicated by the fact that the behaviour of individual immune components can have both positive and negative effects. As the inconsistent TLR findings discussed previously suggest, researchers need to consider how each component interacts with other aspects of the immune system. Considering that HIV disease feeds on immune activation, the ultimate goal is a plan for deploying the various immune defences to provide maximum effectiveness with the least extraneous activity.

Manipulation of the immune system may eventually prove useful in further restoring the immune system after the antiretroviral agents have reduced HIV to undetectable levels. In particular, enhancing the anti-HIV immune response promises to help block residual HIV, perhaps allowing for simplification or elimination of drug therapy. In addition, immune therapy may prove more effective before the body ever comes in contact with HIV. Vaccines and other preventive technologies have so far been unable to block HIV transmission. Selectively stimulating appropriate immune responses could prove vital to advancing such prevention efforts.

Clinical Research, Treatment and Care

AIDS 2008, of course, took place two years before the deadline for universal access, and significant attention was devoted to the theme of the conference: Universal Action Now!, particularly in the context of both increases in the pace of scaling up treatment and care interventions and the growing realization that few countries are on target to meet universal access goals. Strategies for improving access to care in resource-limited countries, the risk of antiretroviral

resistance in these countries, and evolving antiretroviral tactics dominated the AIDS 2008 agenda on clinical research and treatment of HIV infection.

Should ART Start at a Higher CD4 Count?

As AIDS 2008 began, an international panel of treatment experts convened by the IAS-USA updated antiretroviral treatment guidelines for adults. The panel recommended broadening options for starting ART at a CD4 count above 350 cells/mm³ and to include people with active hepatitis B or C infection, cardiovascular disease risk, or compromised kidney function.²⁷ The panel set no upper CD4 limit on when treatment should begin. A growing data stream from recent trials suggests that earlier ART may ward off not only AIDS-defining diseases, but also non-AIDS cancers and heart, liver, or kidney diseases.^{28,29,30}

A cohort study at AIDS 2008 added to accumulating evidence favouring earlier ART. This 1,679-person analysis of the US HIV Outpatient Study cohort found that a CD4 count under 350 cells/mm³ when first measured independently raised the risk of new cardiovascular disease more than 75%.³¹ Additional evidence supporting the clinical value of earlier intervention with antiretrovirals could lead World Health Organization (WHO) advisors to review guidelines on when to start ART in resource-limited countries. WHO currently recommends ART for anyone with a CD4 count below 200 cells/mm³, while suggesting clinicians should “consider treatment” for people with 200 to 350 cells/mm³ and defer treatment for people with more than 350 cells/mm³.³²

During AIDS 2008 incoming IAS President Julio Montaner predicted that revamped treatment guidelines for high-income countries could “revolutionize the treatment of HIV” by recognizing HIV infection as a chronic inflammatory disease that “affects the heart, liver, kidneys, and in due course we are going to learn the rest of the assorted organs in the body.”^{33,34} Montaner cautioned that raising the CD4-cell threshold for starting ART could further widen the treatment-access gap between developed and developing countries unless experience confirms his modeling study, which suggests that expanding ART access will help limit the growth of the HIV epidemic and its associated costs by reducing infectivity. If this hypothesis proves true, the preventive effect of ART will be a powerful new argument for rolling out antiretroviral therapy more aggressively.³⁵

Related to the growing debate regarding optimal start and switch times is the issue of how and what information to use in clinical decision-making regarding switching drug regimens. A Haitian study raised concerns about relying on clinical or immunological criteria to detect ART failure, based on WHO treatment guidelines, in the absence of VL and CD4+ laboratory monitoring. In this study almost

half (47%) the participants had HIV RNA levels below the limit of detection after being assessed as failing ART using clinical criteria, suggesting that the lack of VL PCR and other laboratory diagnostics in clinical decision-making could lead to premature switching.³⁶

When to Start ART in TB Co-infected Patients

In many parts of the world, tuberculosis is the first AIDS diagnosis and a leading cause of death among people living with HIV. Yet the best time to start ART in HIV/TB-co-infected individuals remains controversial. Two studies presented at AIDS 2008 – one in Brazil and one in Argentina – addressed this question but did not reach the same conclusion.

Valéria Saraceni’s 632-person analysis of THRio, a Brazilian observational cohort study, found that starting ART *at any point* after beginning anti-TB therapy independently halved the risk of death, while completing the course of anti-TB drugs independently lowered the risk of death more than 85%.³⁷ (Figure 6). A study of 142 HIV/TB co-infected people in Argentina recorded a higher overall death rate in those beginning ART within 8 weeks of starting anti-TB medications compared with those starting ART later (14.4% versus 6.8%, $P = 0.013$).³⁸ However, TB-related mortality was the same in the two groups, a pre-ART clinical AIDS diagnosis was twice as common in the early-ART group, and the investigators did not perform multivariate analyses to determine whether the timing of ART affected mortality independent of other risk factors. Both of these studies were observational; ongoing randomized trials to address the optimal time to start ART during TB treatment are ongoing.

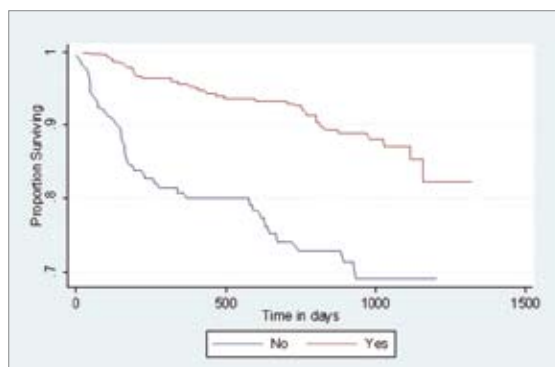


Fig 6. Kaplan-Meier: Survival After a TB diagnosis, by exposure to HAART (Log-rank test- $p < .001$)

Source: Saraceni, V et al. Tuberculosis, HAART use and survival in the THRio Cohort, Rio de Janeiro, Brazil. (MOAB0305)

The Brazilian study linked delayed HIV diagnosis in TB patients with a lower chance of receiving ART. That finding underscores the critical need to integrate HIV and TB care, a policy emphasized in the WHO/IAS/Global Fund/World Bank consensus statement on knowledge gaps in the public

health approach to delivering ART and care.³⁹ The Brazilian investigators recommended universal opt-out HIV testing for everyone with TB. UNAIDS already recommends HIV testing and counselling for all TB patients and screening of all HIV-infected people for TB. Because TB is such an important co-morbidity throughout the world, more rigorous prospective research is needed to optimize the role of ART for co-infected people.

In a post-conference development related to this issue, the South African chief director of HIV and AIDS, Dr Nomonde Xundu, confirmed that, as a result of evidence presented at the conference, a recommendation was under discussion about potential changes to South Africa's national treatment guidelines, including whether to recommend earlier initiation of ART, and whether additional clinical guidance for individuals co-infected with TB is also required.⁴⁰

Task Shifting to Widen Access to Care and Treatment

Acute shortages of health professionals remain a stumbling block to wider HIV care in many low-income countries. New research presented by several groups at AIDS 2008 examined the role of task shifting – transferring certain physician responsibilities to other health workers – as a way to improve overall access to care.

In Malawi's rural Thyolo district, shifting some counselling work from nurses to lay counselors – then shifting ARV initiation duties from physicians to nurses – helped the region reach universal access targets.⁴¹ The region has 600,000 people with HIV infection, including 9,000 to 12,000 who urgently needed antiretrovirals, when task shifting began. Médecins Sans Frontières set an initial target of treating 10,000 people. Shifting antiretroviral care duties away from physicians more than doubled the number of people tested for HIV, and, from 2004 through 2007, boosted the number of people starting ART from 2,000 to 12,000 (Figure 7). Universal access in Thyolo cost 3 Euros per district inhabitant per year.

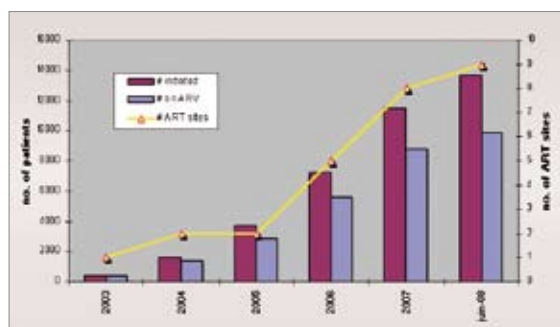


Fig 7. ART Initiation in Thyolo District 2003-2008

Source: Massaquoi, M et al. Achieving universal access to antiretroviral therapy in a rural district in Malawi: how was it done? (TUAB0303).

A study comparing nurse-led primary care-based ART with specialist hospital-based care in rural Swaziland documented lower mortality in the nurse-led setting and comparable dropout rates. A separate modeling study predicting the impact of a pilot task-shifting project in Rwanda estimated that the number of physicians needed to provide ART by the end of 2008 will drop from 77 physicians working 30 hours per week to 17 physicians working the same number of hours. That change represents a 78% decline in physician demand for HIV care and a 183% gain in physician capacity for non-HIV care (Figure 8).

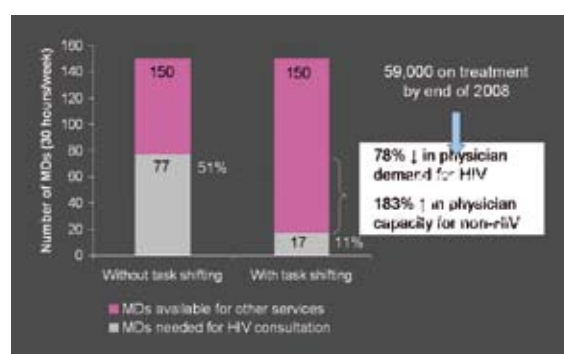


Fig 8. Roll Up to National Level

Source: Chung, J et al. Quantification of physician-time saved in a task shifting pilot programme in Rwanda. (WEAB0205)

Task shifting to nurses will not solve ARV access problems in sub-Saharan Africa because the region also suffers from a severe shortage of nurses. However, as the study in Malawi found, certain nursing tasks can be assigned to other workers, and greater community involvement can also expand HIV care.⁴⁴ By showing that task shifting may free physicians to manage other diseases, the Rwandan study demonstrates that robust AIDS funding need not mean neglect of other pressing clinical issues.⁴⁵

Risk of Resistance in High-prevalence Countries

With respect to ART, one of the most important AIDS 2008 studies assessed the emergence of resistance-related mutations in Malawi sites that rely on CD4 counts and clinical symptoms to assess treatment response – because routine viral load monitoring remains too expensive.⁴⁶ Resistance testing of samples from 96 people whose first ARVs failed uncovered an array of mutations that could severely compromise nucleoside use in second-line regimens.

Viral load monitoring would have detected ARV failure earlier and prevented the emergence of many mutations that developed while these patients continued a failing regimen. But viral load testing – and often CD4-cell assays – remain rare in many resource-poor clinics, and their absence limits optimal ART. Second-line antiretrovirals are more scarce than

first-line agents in many of these same regions, and rampant resistance will threaten their use.⁴⁷ A recent modeling study by A Phillips suggested that tracking symptoms and CD4 counts may do as well as viral load testing in increasing potential life-years survived in low-income countries.⁴⁸ But that analysis may have underestimated the impact of certain mutations detected in the Malawi study.

A 2008 consensus statement by WHO, IAS, World Bank and the Global Fund underscored the need to prioritize research to address two concerns raised by this study – determining the optimal time and criteria for switching to second-line therapy, and defining the most appropriate use of viral load and CD4-cell monitoring in resource-constrained regions.⁴⁹ The answers to these questions will be key in shaping the “second wave” of ART rollout and the clinical approach to treatment and care in low- and middle-income countries.

Trials of Preferred ARV Regimens

Many randomized ARV trials recruit patients from across the globe. Often, however, these trials enrol patients from the same well-established clinics in low- and middle-income countries. Rigorously testing promising ARV tactics in diverse settings is critical to establishing their value in countries with differing demographics and standards of care. Two ongoing trials tackling this issue were presented at AIDS 2008.

The multinational PEARLS trial led by the US AIDS Clinical Trials Group set out to compare three first-line regimens in 1,361 adults in Brazil, Haiti, Peru, Malawi, South Africa, Zimbabwe, India, and Thailand, and 210 adults in the United States.⁵⁰ Patients randomized to once-daily didanosine, emtricitabine, and atazanavir (without a ritonavir boost) had a higher risk of treatment failure after 72 weeks than patients randomized to twice-daily zidovudine plus lamivudine and once-daily efavirenz (Figure 9). Failure rates differed from country to country and were higher among people with prior or current tuberculosis. Two points stand out: First, the atazanavir regimen failed by viral load criteria before clinical failure criteria became statistically significant – a finding emphasizing the value of viral load monitoring. Second, although atazanavir is licensed for use with or without ritonavir, most patients in the US and Western Europe take the drug with ritonavir to keep atazanavir concentrations even.

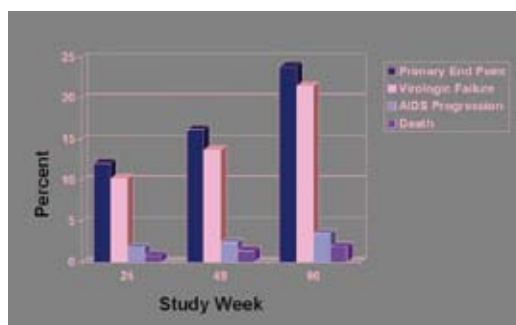


Fig 9. Cumulative Probability of Treatment Failure ddi-EC+FTC+ATV

Source: Campbell, T et al. ACTG A5175: a multinational study of ddi-EC, FTC and atazanavir vs. co-formulated AZT/3TC and efavirenz for initial treatment of HIV-1 infection. (THAB0404)

In a recent US trial published before the conference an efavirenz-based combination controlled HIV better than lopinavir/ritonavir in previously untreated people, even in those starting ART with a viral load above 100,000 copies/mL.⁵¹ A 48-week Mexican trial led by independent investigators confirmed better viral control with efavirenz than with lopinavir/ritonavir in ARV-naïve people with advanced HIV infection (Figure 10).⁵² The Mexican study enrolled only patients with fewer than 200 CD4 cells/mm³, and the median pre-treatment count stood well under 100 cells/mm³. Discovery of compelling country-specific results in such studies should inspire further randomized controlled trials outside high-income countries.

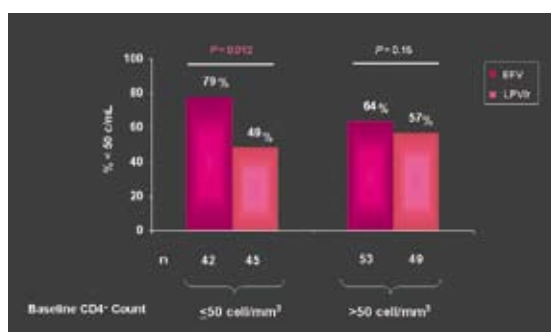


Fig 10. Virological Suppression Stratified by Baseline CD4+ Counts (>= 50 cell/mm³)

Source: Madero, S. et al. A prospective, randomized, open label trial of efavirenz versus lopinavir/ritonavir based HAART among antiretroviral therapy naïve, HIV infected individuals presenting for care with CD4 cell counts. (TUAB0104)

Prevention Research

Research into new HIV prevention technologies in the years leading up to AIDS 2008 has been discouraging. Between 2006 and 2008, five advanced stage trials (four for broad-spectrum microbicides and one for a vaccine) announced nil or negative results, and there are currently no vaccine candidates ready for field-testing. The long-term circumcision results reported at AIDS 2008 indicated that prevention interventions do have the potential to substantially reduce new infections. Other presentations mapped out prevention strategies using antiretroviral agents, which could be introduced in the field relatively quickly.

More Evidence that Circumcision Works

Most optimistically, Robert Bailey reported results from extended follow-up of participants in their randomized controlled trial of male circumcision in Kisumu, Kenya at a late-breaker session. Previously, participants in the three trials of circumcision had data up to only 21 – 24 months post-randomization. Now, with the inclusion of 42 months of follow-up, Bailey and his colleagues reported a 65% protective effect of circumcision against HIV acquisition in young men in Kisumu (Figure 11). The Kisumu trial also attempted to gauge the effect of circumcision on sexual pleasure and performance. They found that there was no appreciable difference between circumcised and uncircumcised men in their reports concerning various measures of sexual function and satisfaction of female partners.⁵³

Bertran Auvert presented the results of a study subsequent to his group's circumcision trial in Orange Farm, South Africa. After counselling 1,207 men on safe sex and treating them for sexually transmitted infections, the researchers offered free circumcisions in a medical clinic. Among the uncircumcised men (68% of the total), 65% eventually accepted the offer.⁵⁴

Auvert's group and the Kisumu trial also attempted to gauge the effect of circumcision on sexual pleasure and performance. They found that there was no appreciable difference between circumcised and uncircumcised men, according to reports from both males and females.⁵⁵

Fred Sawe in addition reported that HIV prevention and reproductive health training was very well received during traditional male rites of passage in the Great Rift Valley.⁵⁶ These ceremonies include circumcision. In the interest of safety, medically trained personnel are increasingly invited to perform the actual circumcisions during maturation ceremonies.

Auvert presented the results of the first circumcision randomized clinical trial three years ago at the 3rd IAS

Conference on HIV Pathogenesis and Treatment in Rio de Janeiro.⁵⁷ Studies began reporting a correlation between higher circumcision rates and lower HIV in parts of Africa 20 years ago.⁵⁸ WHO has since then developed a "Male Circumcision Quality Assurance Guide" providing a framework for safe mass circumcision programs, including infection control and risk reduction guidelines.⁵⁹ Yet there are still no large-scale circumcision programmes for high HIV prevalence areas. Richard White presented a model predicting that in sub-Saharan Africa, the lowest cost per HIV infection averted in the next ten years, around US\$1,000, would occur if the target circumcision age group were 25-34 year-olds.⁶⁰ This is the male age range with the highest immediate HIV risk and somewhat older than the WHO recommended target group (12-30 year-old males). White and a poster presented by Agnes Binagwaho advocated also circumcising newborns, although the benefits of doing so would not be visible for approximately 25 years.⁶¹

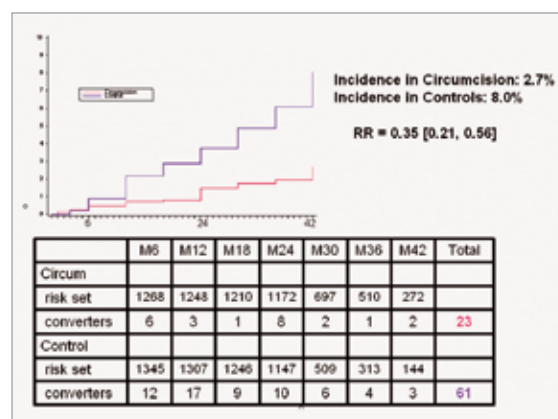


Fig 11. Cumulative HIV Seroincidence over 42 Months by Circumcision Status

Source: Bailey, RC et al. The protective effect of male circumcision is sustained for at least 42 months: results from the Kisumu, Kenya trial (THAC0501).

Harnessing Antiretroviral Treatment for Prevention

While the implementation of circumcision as a viable prevention strategy lags, a debate has emerged about using antiretroviral therapy as a prevention tool. In January 2008, Switzerland's Federal Commission on AIDS-Related Issues (EKAF) released a statement indicating that people living with HIV who were taking an effective (maximally suppressive) antiretroviral regimen could not transmit the virus.^{62,63} There were several strict conditions attached to that position, including at least six months of undetectable viral load, no other sexually transmitted disease, and ensuring HIV-negative sex partners were able to make an informed choice to dispense with condoms.

Nonetheless, arguments ensued over the Swiss statement's implications at an EKAF-sponsored satellite symposium that took place just before the official opening of AIDS 2008. EKAF president Pietro Vernazza presented his Commission's point of view, which places the position in a very carefully-defined context.⁶⁴ He said that EKAF was merely standardizing what physicians were already telling their patients. In addition, Swiss law is very strict about exposing other people to HIV, even if transmission does not occur. Vernazza's point was not that the risk of transmission under suppressive therapy was nil, rather that it was very small, comparable with the risk of transmitting while using condoms. Successful ART should therefore be a reasonable defence against laws criminalizing HIV exposure.

Suzanna Attia presented the results of a meta-analysis of studies investigating transmission risk under ART.⁶⁵ There have been no studies of patients on successful ART or in men who have sex with men. There have been a few studies concerning HIV-discordant heterosexual couples in which the HIV-positive partner has an untreated viral load below 400 copies/mL. One transmission was noted in a total of approximately 900 patient-years. Information on condom use and sexually transmitted infections in these studies was unavailable. Attia argued for further research before drawing any conclusion.

A randomised controlled trial is currently under way to quantify the relationship between the level of treatment-suppressed viral load and HIV transmission. The trial, sponsored by the US National Institutes of Health, will follow 1,750 HIV sero-discordant couples assigned to immediate or

deferred treatment. Results will not be available before 2016, a problematic timeline given the research suggesting that persons with treatment-suppressed HIV are already reducing their condom use.⁶⁶

The Tantalizing Promise of PrEP

In addition to viewing ART as a potentially effective prevention modality involving those already infected, at the conference there was also discussion of administering ART as pre-exposure prophylaxis (PrEP) for HIV-negative persons who are at high risk for infection, including members of HIV-discordant couples.⁶⁷ Although it faced some activist opposition in the first round of Phase III clinical trials, when some trials were prematurely halted, support for the concept has grown, no doubt at least partly due to the failure of several other biomedical prevention modalities and improvements in the engagement of civil society in the design and implementation of PrEP clinical trial protocols.

There are a number of on-going and planned PrEP trials testing daily regimens (Figure 12). Although PrEP was first discussed in the mid 1990s, it will be at least four more years before we see PrEP's benefits fully evaluated in several populations using multiple dosing strategies. The utility of intermittent pre-coital regimens is only now coming under consideration.^{68,69} There was one preliminary human trial reported at AIDS 2008 involving long-term injectable PrEP. This trial found that an intramuscular sustained-release form of rilpivirine (TMC278, a new reverse transcriptase inhibitor nearing licensure for HIV treatment) could deliver protective drug levels for over 12 weeks.

Sponsor/Study Name	Expected Results	Product(s) Tested	Sites	Status	Study Population
CDC: <i>Tenofovir Extended Safety Study</i>	2009	Tenofovir	USA (N=400)	Fully enrolled	MSM
NIH: <i>MTN-001</i>	2009	Tenofovir Tenofovir vaginal gel/Both	South Africa, Uganda, US (N=144)	Enrolling	Women
CDC: Bangkok Tenofovir Study	2009-2010	Oral tenofovir	Thailand (N=2400)	90% enrolled	Male and female injection drug users
CDC: <i>TDF-2</i>	2010	Tenofovir + emtricitabine	Botswana (N=2000)	Enrolling	Heterosexual men & women
NIH, Univ. Calif., Gates Foundation: <i>iPrEx</i>	2010	Tenofovir + emtricitabine	Brazil, Ecuador, Peru, US, other (N=3000)	Enrolling	MSM
Univ. Washington, Gates Foundation: <i>Partners PrEP</i>	2011	Tenofovir Truvada	Kenya, Uganda (N=3900 couples)	First sites activated	HIV-discordant heterosexual couples
NIH: <i>VOICE</i>	2012	Tenofovir Tenofovir + emtricitabine Tenofovir vaginal gel	Malawi, South Africa, Uganda, Zambia, Zimbabwe (N=4200)	Not yet enrolling	Women
Family Health International: <i>FEM-PrEP</i>	2012	Truvada	Kenya, Malawi, South Africa, Tanzania (N=3900)	Not yet enrolling	Women

Fig 12. Current PrEP Trials

Source: Mastro, T. *Pre-exposure prophylaxis: Overview of current and planned trials.* (THSY0603)

There are obvious safety and economic concerns about supplying antiretroviral drugs to large HIV-negative populations. If it proves effective, topical application to genital and anal areas might be more feasible. As conference attendees heard, tenofovir gel applied locally yields vaginal drug concentrations 100- to 1,000-fold higher than systemic oral administration.⁷¹ In contrast, blood plasma concentrations are more than 10-fold lower with the gel.

Topical microbicides have not performed well in human HIV prevention studies, with 10 trials of surfactant and polyanionic compounds yielding negative results. These non-specific, broad-spectrum compounds inactivate bacteria, viruses and even sperm by emulsifying (surfactants) or coating (polyanions) their outer layers.

The field is clearly moving forward. AIDS 2008 marked the shift from broad-spectrum to antiretroviral microbicides.^{72,73} Besides the VOICE study testing oral PrEP versus tenofovir gel, another large, advanced-stage trial will start in the next two years. This is IPM009, still in its planning phase. It will study the efficacy of the reverse transcriptase inhibitor dapivirine, either as a short-acting vaginal gel or as a long-lasting vaginal ring. The latter is a new, innovative mechanism for delivering anti-HIV microbicides. IPM009's sponsor, the International Partnership for Microbicides, eventually plans to combine dapivirine with the licensed entry inhibitor maraviroc.

But the results of many of these trials are not expected until 2010-12. The only encouraging microbicide *in vivo* results at AIDS 2008 came from a small macaque trial of a vaginal gel, combining two antiretrovirals, tenofovir and emtricitabine. The trial applied this combination gel 30 minutes before exposure to HIV. Six out of six macaques were protected from 20 vaginal challenges over ten weeks. In contrast, seven of eight control macaques became infected after a median of 3.5 challenges.⁷⁴

Vaccines: The Role of Protective Immunity

Recent setbacks in both the vaccine and microbicides field have required a refocus of research efforts in both fields. At the conference, Seth Berkley reviewed the International AIDS Vaccine Initiative's (IAVI) efforts to screen human subjects for broadly neutralizing antibodies against HIV.⁷⁵ These antibodies would prevent new cells from becoming infected and might be the key to a vaccine that creates "sterilizing immunity" against a wide variety of HIV isolates. Berkley says that advanced mass screening techniques have now permitted IAVI's antibody project to select promising candidates. Even if such antibodies were isolated in a few individuals, the problem would remain how to induce them in the entire human population. A vaccine based on these antibodies is not expected soon. Berkley also promoted the

concept of using replicating viral vectors. These vectors would consist of a carrier virus containing recombinant HIV genes that would induce a potent immune response.

Current HIV vaccine vectors are all nonreplicating. Among these is the adenovirus vector used in the Merck vaccine that yielded negative results in the well-known STEP trial terminated last year. A US National Institutes of Health study comparing chimpanzee responses to replicating and nonreplicating adenovirus-based HIV vaccines was one of the early warnings about the Merck vaccine design.⁷⁶ The replicating adenovirus vector elicited markedly superior immune responses. Switching to live vectors now will entail considerable delay as various technical and safety concerns are resolved.

A New Emphasis on Prevention Cocktails or "Combination Prevention"

Combination prevention strategies was a popular topic of discussion at the conference.⁷⁷ Circumcision programmes can be combined with condom promotion and other structural and socio-behavioural approaches to preventing HIV. More detail on combination prevention is outlined in the following section.

As the Kisumu trial results show, circumcision alone will not eradicate HIV incidence in men. There is some optimism that adding antiretroviral agents in one of the forms described above may have a major impact in reducing incidence. Research is moving forward slowly despite this potential, and mass implementation will likely also be slow, if the circumcision experience is any example. The prevention research legacy of AIDS 2008 is an increasing recognition that fulfilling the promise of emerging prevention technologies requires a renewed sense of urgency.

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