IAS2009
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IMPACT REPORT

Summary of Key Research and Implications for Policy and Practice

5th IAS Conference
on HIV Pathogenesis, Treatment and Prevention
19-22 July 2009, CapeTown • www.ias2009.org

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Activists demonstrate against recent reports of interruptions in drug supplies and shortages.

INTRODUCTION

Attracting more than 5,800 participants from 123 countries, the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2009), held from 19 to 22 July 2009 in Cape Town, South Africa, offered more than 1,550 reports on original research in four areas: Basic Sciences (Track A), Clinical Sciences (Track B), Biomedical Prevention (Track C), and – new at this meeting – Operations Research (Track D). The 59 sessions included 12 plenary addresses by leaders from every sector of HIV research. The conference was particularly rich in research that may affect the path of the epidemic in low- and middle-income countries, though policy and practice-shaping developments from high-income countries were hardly ignored.

Consistent with the focus of the pathogenesis conference series, this report aims not only to highlight particularly important original research and other developments detailed at IAS 2009, but also to analyze their potential impact on policy and practice in the coming years for those working in HIV or related fields. Throughout the conference and in the closing session, four teams of rapporteurs summarized all oral and many poster presentations, and discussed their relevance in the context of ongoing research. This review of all four conference tracks draws upon these rapporteur summaries, outlines important findings from additional studies, and where relevant, outlines other recently published scientific literature. The report includes abstract numbers of cited presentations linked to online files of slides, posters or abstracts, as available. A full abstract search of IAS 2009 and earlier IAS conferences is available on the IAS website at www.iasociety.org.

At the opening of IAS 2009, International AIDS Society (IAS) President and IAS 2009 Conference Chair Dr. Julio Montaner, Director of the BC Centre for Excellence in HIV/AIDS in Vancouver, Canada (right), said "Good science must inform good policy and programming to ensure the best outcomes for individuals and communities." Conference Co-Chair Prof. Hoosen Coovadia, Chairman of Dira Sengwe and Scientific Director of the Doris Duke Medical Research Institute at the University of KwaZulu-Natal in Durban, South Africa, said "IAS 2009 is an ideal opportunity to move both the national and global responses to AIDS forward, based on sound science."

EXECUTIVE SUMMARY

New data presented at IAS 2009 is already having an impact on HIV policy and practice on a global scale.

- Results of several basic research studies provided the field with a better understanding of the elevated HIV infection risk among African women due to chronically activated T-cells in genital tract mucosa, how complex genetic variables may affect HIV acquisition and disease progression, and how early antiretroviral therapy (ART) can substantially reduce the size of latent HIV reservoirs, a significant clinical issue in chronic HIV infection.
- Data from a study demonstrating that pre-ART inflammation and coagulation markers predict death on ART, and related findings showing that HIV replication induces activation of tissue factor pathways, thrombosis and fibrinolysis (with associated increases in mortality), underscored an emerging "paradigm shift" in our understanding of HIV disease progression and the role of inflammation.
- Findings demonstrating that maternal triple-drug ART used throughout pregnancy and breastfeeding reduced vertical transmission to 1% (and also lowered the risk of prematurity, stillbirth and abortion) are expected to inform revised World Health Organization (WHO) and South African national guidelines on antiretroviral prophylaxis.
- Research delineating the impact of antiretroviral therapy on reducing coincident tuberculosis and malaria epidemics in HIV-prevalent regions argued for wider and earlier access to treatment; by the end of the conference South African health authorities indicated that they would consider providing ART to everyone co-infected with TB and HIV.
- In the biomedical prevention field, new research helped define the impact of pregnancy on the risk of HIV transmission among serodiscordant couples.
- New data also showed an apparent lack of a direct effect of male circumcision on HIV acquisition in female partners.
- An updated presentation of a WHO modelling study, which suggests that universal voluntary testing and immediate ART could turn the tide of the epidemic, was bolstered by additional data from recent studies demonstrating the potential preventive impact of ART at a population level. This calls for efforts to elaborate the significant challenges of making such a strategy operational.
- A study indicating that early ART intervention for everyone with CD4+ counts of below 350 cells/mm3 cells/μL was more cost effective than deferred ART intervention added to the growing scientific consensus that normative guidance should advise earlier ART initiation; this is particularly clear considering the recently suspended Comprehensive International Program of Research on AIDS (CIPRA) HT001 trial in Haiti, which found substantially higher rates of mortality and morbidity in the deferred versus early ART intervention arm.
- Operations research presented at the conference provided important new insights into how integrating HIV with other health services and using a variety of service delivery approaches (including deploying trained community or lay workers) can exponentially expand health system capacity without compromising standards of care or treatment outcomes.
- Results from the five-year Development of Anti-Retroviral Therapy in Africa (DART) trial comparing laboratory CD4+ and viral load monitoring to clinical monitoring found minimal differences in virologic outcomes but substantially higher costs associated with laboratory monitoring; these and other data from IAS 2009 suggest that CD4+ count monitoring is cost effective as a targeted – rather than routine – strategy.
- A provocative overview of AIDS financing suggested that much more could be done to get "less AIDS for the money" by ensuring that interventions are evaluated more consistently for efficacy and cost effectiveness, and strategically targeted for maximum benefit.

IAS' Immediate Past President Pedro Cahn giving a plenary presentation, Antiretroviral Treatment in 2009: Successes and Challenges.

TRACK A: BASIC SCIENCES

Summarizing Track A reports, lead rapporteur Wendy Burgers (University of Cape Town) highlighted invited lectures on viral reservoirs and eradication, immune activation, acute infection and cellular immunity [1]. In the first of those four fields, Jean-Pierre Routy (McGill University, Montreal) analyzed strategies to mobilize reservoirs that contain virus beyond the reach of standard antiretroviral therapy [2], including studies of valproic acid, histone deacetylase inhibitors and NF-kappa-B-independent activators. He also reviewed work on interleukin-7 as an agent to prevent viral latency and promote immune reconstitution.

Routy concluded that early ART "represents the easiest intervention to control reservoir size", a concept explored further by Joep Lange (University of Amsterdam) [3]. Lange noted that a seminal study of viral decay rates estimated it would take 7.7 years of suppressive ART to eliminate HIV from latent reservoirs [4]. But Lange maintained that treatment soon after infection could make those reservoirs smaller. In an observational study, all nine patients who began ART before HIV seroconversion and six of eight who began within six months of seroconversion had no detectable virus in cell reservoirs, compared with all 17 comparison patients who began ART during chronic HIV infection [5].

In a scientific keynote address, Nobel Laureate Françoise Barré-Sinoussi (Pasteur Institute, Paris) addressed the issue of viral persistence in cellular reservoirs [6]. She proposed that ART may need to be started earlier in the course of infection and followed with a discussion of strategies that restore the immune system (to prevent immune senescence) and that target residual infected cells (to limit residual disease). Barré-Sinoussi, an IAS Governing Council member, will chair a two-day basic science workshop on controlling HIV reservoirs before the next International AIDS Conference, scheduled for July 2010 in Vienna, Austria.

IAS 2009 also featured several compelling studies on genetic and cellular research affording new insights on HIV infection risk in African women, viral loads in HIV-1 subtype C-infected people, breast milk transmission of HIV, and overall vertical transmission risk.

Biological Factors behind HIV Susceptibility and Vertical Transmission

Comparing women in Kisumu, Kenya, and San Francisco, USA, Craig Cohen (University of California, San Francisco) documented higher proportions and numbers of activated CD4 cells – the primary target of HIV – in the genital tracts of women in Kisumu [7]. Until this study, the higher HIV risk in African women than in women elsewhere and in African men has been attributed primarily to sociobehavioural and gender norms and to high rates of sexually transmitted infections (STIs). This study of 18- to 24-year-old women without HIV or other STIs found significantly higher levels and/or proportions of seven activated T-lymphocyte subtypes, including activated CD4 and CD8 cells. Compared with the 18 women in San Francisco, the 36 in Kisumu also had significantly higher concentrations of a cytokine that favours HIV transmission and significantly lower concentrations of two immune factors that protect from HIV. The investigators speculated that higher levels of activated T-lymphocytes in African women may reflect their greater exposure to pathogens, including parasites and viruses.

Innovative research by Romain Marlin (Pasteur Institute, Paris) showed that cells of the maternal uterine mucosa efficiently transfer HIV-1 to other cells, such as placental cells [8]. Yet HIV-1 transmission remains rare in utero, especially during the first trimester. To evaluate viral susceptibility and transmission in the uterine mucosa, Marlin exposed mucosal cells to HIV-1 that uses the CCR5 coreceptor or the CXCR4 coreceptor. The tissue tested came from HIV-negative women who had undergone elective abortions. CD14-expressing cells proved the main target of CCR5-using HIV-1, the type of virus usually involved in HIV-1 transmission. Although infected CD14 cells produce low levels of virus, they efficiently transfer virus to other cells. What stifles viral transmission from the uterine mucosa to the placenta remains a mystery. Discovering the factor or factors involved in preventing that transmission could offer clues that are important to other areas of prevention research.

Nobel Laureate Françoise Barré-Sinoussi (Pasteur Institute, France), giving the keynote scientific plenary at IAS 2009. Barré-Sinoussi, an IAS Governing Council member, will chair a two-day basic science workshop on controlling HIV reservoirs before the next International AIDS Conference, scheduled for July 2010 in Vienna, Austria.

Enhanced Collaborations on HIV/TB Research and Programming

At the IAS 2009 pre-meeting, "Catalyzing HIV/TB research: innovation, funding, and networking", more than 200 researchers, implementers and HIV and TB advocates discussed the need for a more customer-oriented approach to the diagnosis and treatment of HIV and TB; one that extends beyond health facilities and engages the broader community. The meeting highlighted promising research on improved TB diagnosis and exciting news of the first new TB vaccine trial, begun recently in South Africa. At the same time, participants emphasized that the extremely limited access to a point-of-care TB diagnostic (dipstick TB test) is undermining efforts to stop TB and represents the single most important research priority today.

The meeting was organized by the World Health Organization and the HIV/TB Working Group of the Stop TB Partnership in collaboration with the IAS, the Consortium to Respond Effectively to the AIDS/TB Epidemic, Treatment Action Group and the Desmond Tutu HIV Centre.

Genetic and Cellular Variables Affecting HIV Progression and Vertical Transmission

In a study of 427 ART-naive Zulu and Xhosa people infected with HIV-1 subtype C, the most prevalent subtype in the world, Boris Julg (Ragon Institute, Boston, and University of KwaZulu-Natal, South Africa) found that the 16 individuals (4%) expressing the HLA DRB1*1303 allele had significantly lower viral loads than people without that gene (about 8,500 versus 43,000 HIV-1 RNA copies/mL) [9]. The correlation held true after statistical adjustment for expression of HLA B57. (HLA class II molecules are involved in the presentation of antigens to T cells.) The protective activity of the *1303 allele did not correlate with increased T-cell functional responses, a finding suggesting that this allele may promote lower viral loads by some alternative mechanism.

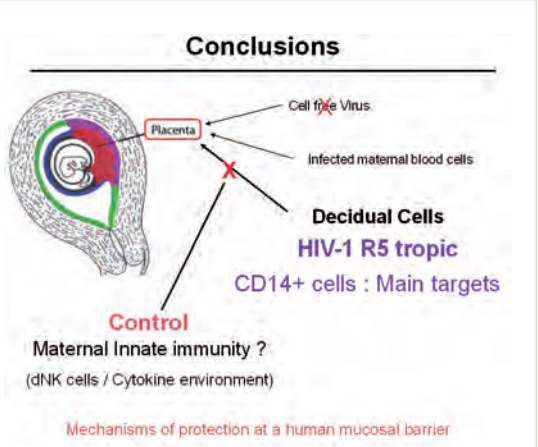
A study of lactating women found that CD4 cells latently infected with HIV-1 and isolated in breast milk can be spontaneously activated, even if ART makes HIV-1 undetectable in blood [10]. Diane Valea (Centre Muraz, Bobo Dioulasso, Burkina Faso) determined that all blood and breast milk samples from six women taking ART and nine women taking brief perinatal antiretroviral regimens contained highly activated CD4 T cells that spontaneously secreted HIV-1 antigens and viral RNA, regardless of whether HIV-1 RNA could be detected in breast milk or blood. The findings suggest an unsuspected HIV-1 cellular reservoir that could play a pivotal role in viral transmission to breastfed infants.

In addition to maternal variables that affect risk of vertical transmission, genetic factors in infants may heighten their risk of infection, according to a study of 131 Kenyan infants by Robert Choi (University of Washington, Seattle) [11]. Ninety-two infants (75%) had the wild-type allele (C/C) at amino acid position 868 of CD4, 37 infants (19%) had the heterozygous allele (C/T), and two infants (5%) had the homozygous allele (T/T). Thirty infants (23%) became infected, seven of them after one month of age. Heterozygous infants had a two times higher overall risk of HIV infection than wild-type infants, and homozygous infants had a four times higher overall risk. Heterozygosity or homozygosity raised the risk of infection after one month (implicating breast milk transmission) almost six times.

Track A: Implications

The highly productive and clinically relevant basic research presented in Track A underlines the need for greater funding and wider deployment of basic benchwork initiatives in

In ex vivo experiments, HIV-infected CD14 T cells efficiently transferred HIV to uterine mucosal cells [7]. Because HIV transmission remains rare in utero, Pasteur Institute investigators postulated that some still-undefined mechanism protects against transplacental transmission of the virus.



Marlin R, Nugeyre MT, de Truchis C, Berkane N, Gervaise A, Barré-Sinoussi F, Menu E: **Antigen-presenting cells represent potential targets for R5 tropic HIV-1 infection in the first trimester pregnancy human uterine mucosa**. *5th IAS Conference on HIV Pathogenesis, Treatment and Prevention: Cape Town, South Africa. MOAA204.* Slides

Youth performers from the Zip Zap Circus School in Cape Town perform at the opening session.

countries with high HIV prevalence. The finding that women in sub-Saharan Africa have more activated CD4 T cells in genital tract mucosa than US women [7] demonstrates: (1) that basic research can uncover unsuspected HIV risk correlations; and (2) that behavioural and cultural factors may not explain all – or even most –of the heightened HIV risk in certain populations.

The study of uterine mucosal cell susceptibility to HIV-1 illustrates the gaps that remain in understanding vertical transmission of the virus [8]. Uncovering the mechanism that limits vertical transmission in utero, despite apparently efficient cell-to-cell transfer of the virus, could have implications for prevention research beyond vertical transmission.

The finding that an HLA class II genetic factor correlates with lower HIV-1 loads in subtype C-infected people [9] shows that much remains to be learned about how genetic variables in diverse populations affect HIV-1 disease progression. The discovery that HLA DRB1*1303 exerts its influence on viral load independently of T cell functional response emphasizes that wider research in highly affected populations can expand the understanding of innate HIV-specific immunity.

The breast milk study [10] may explain why even suppressive ART does not completely stop HIV-1 transmission via breast milk, although Track B studies, reviewed in the following section, suggest effective therapy can cut breast-milk transmission to less than 1%. Work should continue to

search for alternative vertical transmission prevention strategies in antiretroviral-treated women with or without detectable HIV-1 RNA in blood. Results of the CD4 gene study [11] underline the importance of learning more about genetic cofactors that influence HIV-1 acquisition and progression as potential means of improving prevention and treatment strategies.

Finally, Track A lead rapporteur Wendy Burgers [1] suggested that reported findings that early ART can dramatically decrease the size of the latent HIV reservoir underscore the call for universal treatment from early stages of infection. Numerous studies in Track B add to the already weighty evidence supporting use of ART earlier in the course of HIV infection, particularly in countries that now use a CD4 threshold of 200 cells/μL.

Conference Leaders Urge Continued Momentum Toward Universal Access in the Face of Faltering Commitments

Several plenary speakers and many other presenters focused their remarks on the need to maintain global momentum on meeting universal access targets for HIV prevention, treatment, care and support. Amid a lingering global recession and indications that world leaders are retreating on previous universal access commitments, conference leaders, plenary speakers and many other presenters warned of serious public health consequences resulting from a retrenchment on AIDS. In an opening session keynote address that presaged many subsequent discussions and presentations, AIDS Free World Co-Director Stephen Lewis called upon members of the scientific community to become activists, urging them to lend their public credibility to ongoing advocacy, including efforts to challenge world leaders to meet their universal access commitments.

Such concerns were further reinforced by reports of ARV stock outs in several African countries. In a report released just prior to the conference, Médecins Sans Frontières argued that funding gaps and supply management problems have led to the delay, suspension or risk of suspension of the supply of HIV drugs in South Africa, Malawi, Uganda and elsewhere. The consequences of disruptions in funding and supplies are potentially catastrophic and will most certainly be measured in lives. For those already on treatment, the interruptions or lowering of dosages may lead to treatment failure and will increase the risk of developing drug resistance.

"Despite the recession, the global response to HIV – including the commitment of sufficient resources to achieve universal access to HIV prevention and treatment, fully fund AIDS research and strengthen underlying health systems – cannot be put in a holding pattern," said IAS President and IAS 2009 International Conference Chair Dr Julio Montaner, who is Director of the BC Centre for Excellence in HIV/AIDS in Vancouver, Canada. "If we don't move forward, we will rapidly lose ground. That is the reality we face at this pivotal moment in HIV scale-up," he added.

For Local Conference Co-Chair Dr Hoosen (Jerry) Coovadia, IAS 2009 occurred at exactly the right time and place. "Without a doubt, AIDS occupies a pivotal position in South Africa's history, having helped to frame our country's political, social and economic life in the post-apartheid era," he said. "With reports of interruptions in drug supply and shortages here and elsewhere foremost on our minds, we must ensure that health delivery systems on our continent are effective and adequately funded in order to prevent needless deaths and countless preventable infections." Dr Coovadia is Chairman of Dira Sengwe and Scientific Director of the Doris Duke Medical Research Institute at the University of KwaZulu-Natal in Durban.

TRACK B : CLINICAL SCIENCES

Advances reported in clinical research at IAS 2009 could have a profound impact on global and national policies guiding antiretroviral initiation. Salient studies detailed the effect of triple-drug ART on coepidemic tuberculosis (TB) and malaria and on prevention of vertical transmission. Other work reviewed by Track B lead rapporteur Pablo Tebas (University of Pennsylvania, Philadelphia) detailed progress in understanding the role of inflammation on HIV and non-HIV disease progression, and outlined findings on a potent new integrase inhibitor [12].

Treating HIV can Curb TB and Malaria

A comparison of 2005 and 2008 TB and HIV rates in a well-defined South African township yielded strong evidence that wider ART accounts for a significant decline in TB prevalence [13]. Analyzing TB rates in 762 people surveyed in 2005 and 1,251 surveyed in 2008, Keren Middelkoop (University of Cape Town) found that TB prevalence fell by more than one-third, from 3% in 2005 to 1.8% in 2008, a significant decline in an analysis adjusted for age, gender and HIV status. Decreasing TB prevalence could be traced almost entirely to HIV-positive people in the township, where antiretroviral access expanded greatly from 2005 to 2008. Other potential explanations of the falling TB rate did not withstand scrutiny.

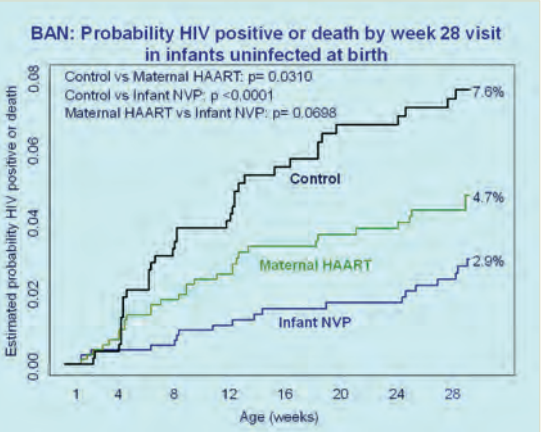
SM Hermans (University Medical Center, Utrecht) determined TB incidence and risk factors in 360 of 7,648 ART-treated Ugandan patients with a new TB diagnosis within two years of starting ART or starting TB drugs within two years of ART initiation [14]. TB incidence fell from 9.91 cases per 100 person years up to three months after starting ART, to 5.14 cases after three to six months, 2.16 cases after six to 12 months, and 0.82 cases after 12 to 24 months. Beginning ART with a CD4 count below 50 cells/µL versus at least 200 cells/µL independently raised the risk of TB by 58% (P=0.01), while male gender indepently raised the risk by 43% (P=0.001). Beginning treatment with efavirenz plus zidovudine/lamivudine versus nevirapine plus stavudine/lamivudine lowered the TB risk by 33% (P=0.002). The association between an efavirenz regimen and lower TB risk is striking because clinicians tend to avoid efavirenz in patients with TB symptoms to avoid switching from efavirenz if the patient has to begin rifampicin for TB.

A prospective Ugandan cohort study traced a steeply declining malaria incidence after ART initiation from 591 cases per 100 person years after one year to 476 cases after two years, 259 cases after three years, and 153 cases after four years [15]. Rogers Kasirye (MRC/UVRI Uganda Research Unit on AIDS, Entebbe) counted 524 new cases of malaria in 1,020 patients enrolled in the DART trial. Pre-ART CD4 count below 10 cells/µL, younger age and less education correlated with a higher malaria risk, while cotrimoxazole prophylaxis lowered the risk.

ART Cuts Vertical Transmission Rate to Less Than 1% During Breastfeeding

In a randomized Botswana trial, triple-drug ART for mothers with HIV lowered vertical transmission during breastfeeding to less than 1%, the lowest rate ever recorded in nursing infants [16]. Roger Shapiro (Harvard University, Boston) and Mma Bana trial colleagues studied 730 women, 560 of them with CD4 count above 199 cells/µL, and randomized to coformulated abacavir/zidovudine/lamivudine or lopinavir/ritonavir plus zidovudine/lamivudine. The remaining women, all with fewer than 200 cells/µL, took nevirapine with zidovudine/lamivudine. All women began ART from 26 to 34 weeks gestation and aimed to continue until six months after delivery, when rapid weaning was advised. Viral suppression rates were greater than 90% with all three regimens at

Three trials [15-17], including the BAN study [16], firmly established the value of maternal ART during pregnancy and breastfeeding in preventing vertical transmission of HIV.



Chasela C, Hudgens M, Jamieson D, Martinson F, Kazembe P, Mofolo I, Long D, Soko A, Smith SB, van der Horst C: **Both maternal HAART and daily infant nevirapine (NVP) are effective in reducing HIV-1 transmission during breastfeeding in a randomized trial in Malawi: 28 week results of the Breastfeeding, Antiretroviral and Nutrition (BAN) Study**. *5th IAS Conference on HIV Pathogenesis, Treatment and Prevention: Cape Town, South Africa.. WELBC103.* Slides

delivery and throughout breastfeeding. Only seven HIV transmissions occurred through six months after delivery for an overall transmission rate of 1%.

Two Track C studies also documented lower vertical transmission rates with maternal ART than with no intervention or other interventions during breastfeeding, including the 2,367-infant randomized Breastfeeding, Antiretroviral and Nutrition (BAN) trial [17], and the randomized Kesho Bora trial involving 805 infants in Burkina Faso and Kenya [18].

First- and Second-line ART for Infants in Resource-poor Settings

Results of a randomized South African trial could reshape early ART planning for infants and children exposed to single-dose nevirapine (sdNVP) at birth if the findings are confirmed [19]. Current national and international guidelines for children exposed to sdNVP call for a first-line regimen, including the protease inhibitors (PIs), lopinavir/ritonavir, because infants infected despite sdNVP often have virus resistant to the nonnucleosides, nevirapine and efavirenz. But nevirapine-based regimens are cheaper and easier to use than lopinavir/ritonavir regimen because nevirapine is formulated with other antiretrovirals as a single generic pill.

The NEVEREST study involved 322 HIV-positive children under two years old who had received sdNVP. Children who reached a viral load below 400 copies/mL after three months of treatment with a lopinavir/ritonavir combination were randomized to continue that regimen or substitute nevirapine for the PIs. Six months after randomization, significantly more children who switched to nevirapine maintained a viral load below 50 copies, although more children who stayed with lopinavir/ritonavir consistently maintained a viral load below 1,000 copies/mL. The NEVEREST investigators believe their results provide "proof of concept that re-use of nevirapine following successful suppression on lopinavir/ritonavir-based therapy is possible under some circumstances for HIV-infected children exposed to nevirapine prophylaxis".

A study of 5,484 children younger than 16 years of age and starting their first ART in sub-Saharan Africa found that only 11.4% met virologic failure criteria – consecutive viral loads above 10,000 copies/mL – more than five months after beginning treatment [20]. (The investigators chose that liberal definition of failure as a starting point in defining failure in children.) Beginning ART with more advanced HIV infection or with ritonavir as the only PI independently raised the risk of failure. Among 146 children remaining in care for at least one year after failure, only 62 (42%) switched to a second-line regimen. Median time between failure and switch was 4.6 months. One year after the switch, only 55% of children had an undetectable viral load.

Research Excellence Recognized at IAS 2009

Six winners of three prestigious scientific awards were presented at IAS 2009.

The **IAS/ANRS Young Investigator Awards** support young researchers (aged 35 years or younger) who demonstrate innovation, originality and quality in the field of AIDS research. Top-scoring abstracts in each track were reviewed by a panel of senior scientists who scored and selected the following winners:

- **Track A: Basic Sciences**
  Renato Aguiar (Brazil/USA) for his abstract, *HIV encapsidates viral genomic RNA and APOBEC3G in mRNA processing bodies.*
- **Track B: Clinical Sciences**
  Max O'Donnell (South Africa), for his abstract, *High Incidence of Multidrug Resistant and Extensively Drug Resistant Tuberculosis among South African Health Care Workers.*
- **Track C: Biomedical Prevention**
  Ashraf Fawzy (Zambia) for his abstract, *Diarrhea morbidity and mortality increases with weaning prior to 6 months among uninfected infants born to HIV-infected mothers in Zambia.*
- **Track D: Operations Research**
  Ingrid Bassett (USA/South Africa) for her abstract *Who Starts ART in Durban, South Africa?... Not Everyone Who Should.*

Young Investigator Prize: Women, Girls and HIV
Linnet N Masese (Kenya) for her abstract, *A Prospective Cohort Study of the Effect of Antiretroviral Therapy on Sexual Risk Behavior in a High-risk Cohort of Kenyan Women.*

IAS TB/HIV Research Prize
Clare van Halsema (South Africa) for her abstract, *Good tuberculosis treatment outcomes and no evidence of increased drug resistance in individuals previously exposed to isoniazid preventive therapy in a population with high HIV prevalence.*

Inflammation Markers Predict Death on ART in South Africa

Higher levels of inflammatory and coagulation markers are strongly related to death from any cause in people taking ART in developed countries [21]. Pre-ART levels of some

of the same markers predicted death after ART began in a randomized trial involving 1,771 members of the South African Defence Force and their dependents [22]. Lotty Ledwaba (Project Phidisa, Pretoria) conducted a case-control comparison nested in a randomized trial comparing different antiretroviral regimens. Matching each person who died (cases) with two people who did not die (controls) by date of randomization, follow-up time, study site and CD4 count, Ledwaba found significantly higher pre-treatment levels of two inflammation markers (C-reactive protein and interleukin-6) and one coagulation marker (D-dimer) in cases. Ledwaba suggested "aggressive clinical monitoring" may be warranted in patients beginning ART with high levels of these markers.

New Integrase Inhibitor Surprises with Potency

Pablo Tebas and the Track B rapporteurs claimed to be "unprecedentedly impressed" with the antiviral activity of S/GSK1349572, an integrase inhibitor with a resistance profile different from those of raltegravir and elvitegravir [23]. A double-blind trial enrolled 35 HIV-positive adults with a viral load above 5,000 copies/mL, no integrase inhibitor experience, and no ART for the past 12 weeks. Study participants were randomized to 10 days of monotherapy with 2, 10 or 50mg of S/GSK1349572 or to placebo. Viral load declined 2.5 log in the 50mg group, more than in any previous antiretroviral monotherapy study. Seven of 10 people taking

50mg had a viral load below 50 copies/mL on day 11, and nine had fewer than 400 copies/mL. Other studies reported at the conference demonstrated limited cross-resistance between S/GSK1349572 and raltegravir, the only marketed integrase inhibitor [24,25].

Track B : Implications

Especially in countries with high TB prevalence, starting ART may raise the risk of clinical TB in the short term because ART-induced immune reconstitution can unmask latent TB by restoring TB-specific immune responses [26]. But two studies at this conference [13,14] found a strong correlation between ART and falling TB rates over the long term. These findings should temper concerns about beginning ART in TB-prevalent countries and, indeed, argue for wider ART access and earlier ART in such populations. As IAS 2009 ended, South African health authorities said they would consider providing ART to everyone coinfected with HIV and TB.

In a similar way, sharply falling malaria incidence throughout the first years of ART [15] bolsters the rationale for wider and earlier ART in populations with high malaria rates. In people not taking antiretrovirals, malaria raises HIV-1 RNA levels [27] and weakens the immune system [28].

Research like this exposes the weakness of arguments against sustained funding of HIV research because it "robs" from studies of other epidemic diseases. Whenever epidemics feed each other – as HIV, TB and malaria do – understanding one can only lead to better control of the others.

Consistently low vertical transmission rates when mothers begin standard triple-drug ART during pregnancy and continue through breastfeeding [16-18] argue strongly for rapid revision of antiretroviral guidelines during pregnancy, delivery and nursing. The World Health Organization is considering these results and others with an eye toward revamping treatment advice, and national guideline bodies should do the same.

The two studies of ART in infants and children break new ground in defining treatment responses in countries with high HIV prevalence. The randomized trial of nevirapine versus lopinavir/ritonavir after viral control with the latter in sdNVP-exposed children offers the first evidence that nevirapine may be a sound treatment option in children already given nevirapine in an unsuccessful attempt to prevent vertical transmission [19]. Nevirapine is less expensive and more convenient than lopinavir/ritonavir, and it usually has fewer long-term side effects – an important consideration for children facing many years of ART.

The study of switching antiretrovirals after first-line failure in children raises several concerns [20]. The nearly five-month average delay between confirmed virologic failure and starting a new regimen could easily open the door to resistant virus, which readily emerges when a failing regimen continues. Yet the delay reflects clinical realities in resource-poor settings, where more time is often needed to confirm failure and to discern the cause. Clinicians may also be less apt to prescribe second-line treatment in clinics with limited second-line options. Results of this important study underscore the need for routine virologic monitoring in low- and middle-income countries and the urgency of providing additional treatment options.

Paula Akugizibwe, regional treatment advocacy coordinator at AIDS and Rights Alliance for Southern Africa, spoke of the need for increased global resources for HIV and TB diagnosis, care and treatment.

The finding that pre-ART inflammation and coagulation markers predict death on ART in South African [22] patients extends similar findings in developed-country cohorts [21] and confirms the need to pursue pathogenic clues among different populations to define similarities and differences. Concordant findings in this area, lead rapporteur Pablo Tebas bluntly concluded, indicate that "inflammation is really important" in understanding disease progression and mortality in people with HIV. In a plenary address on this topic, Wafaa El-Sadr (Columbia University, New York) called the dawning recognition of how uncontrolled HIV permits ongoing inflammation a "paradigm shift" [29]. She cited numerous studies showing that HIV replication induces activation of tissue factor pathways, thrombosis and fibrinolysis, which are all associated with an increased risk of all-cause mortality.

The 10-day monotherapy study of the potent investigational integrase inhibitor, S/GSK1349572, demonstrates the value of continued antiretroviral development [23]. The past few years witnessed the arrival of several strong and tolerable antiretrovirals in new and existing classes. There is no reason to assume that even better drugs cannot be developed.

TRACK C: BIOMEDICAL PREVENTION

IAS 2009 included no major reports on three biomedical prevention fronts – microbicides, pre-exposure prophylaxis (PrEP) or vaccines – although portentous microbicide and PrEP trials are underway. On the vaccine front, Track C lead rapporteur Sinead Delany-Moretlwe [30] (University of Witwatersrand, Johannesburg) reviewed an analysis by José Esparza (Bill & Melinda Gates Foundation, Seattle), who noted that systemic immunity to HIV-1 rarely occurs in nature and may not be possible with a vaccine [31]. Recent work demonstrating rapid viral replication in the mucosa and rapid systemic dissemination suggests research priorities should shift to a mucosal vaccine that elicits an immune response at the viral portal of entry, Esparza argued. The meeting did feature important studies on prevention with ART, circumcision and acyclovir.

ART Impact on Pregnancy Outcome and Risky Sex

Triple-drug ART does more than prevent vertical transmission (as outlined in the Track B discussion); it also lowers the risk of prematurity, abortion and stillbirth among African women [32]. This study of 3,273 pregnant women in Malawi and Mozambique recorded significantly lower mortality among pregnant women who started nevirapine-based ART than in those who did not (0.7% versus 7.4%, $P<0.001$). Leonardo Palombi (DREAM Program, Rome) reported that rates of abortion or stillbirth were 4.3% in the ART group and 25.7% in the no-ART group ($P<0.001$). Regardless of CD4-cell stratum, the prematurity rate was 70.8% lower in women who took antiretrovirals.

A prospective study of 898 female bar workers in Mombasa, Kenya, found no evidence supporting the hypothesis that widespread ART will encourage more risky sex in low-income countries. Indeed, women in this cohort reported safer behaviour after they began ART [33] than before they started. Linnet Masese (University of Nairobi) found significantly higher rates of 100% condom use after ART began and a strong trend toward abstinence or having only one sex partner during ART. STIs were one-third less likely after ART began.

Pregnancy nearly doubled the risk of HIV seroconversion in a two-year study of 500 HIV-discordant couples in Kisumu, Kenya [32].

Comparison of those who conceived with those who did not

	Pregnancy (N = 373)	No pregnancy (N = 698)	p-Value
Median age in years (IQR)	27 (24-32)	34 (27-44)	<0.01
Median number (IQR) of children with study partner	1 (0-3)	2 (0-4)	0.01
Median number (IQR) of years with study partner	4 (2-7)	6 (2-7)	<0.01
Percent of women HIV infected	56	63	0.10
Median CD4 count/mcL (IQR) of HIV infected partner	477 (349-615)	429 (331-623)	0.12
Percent of individuals who seroconverted	10.8	5.9	0.046

RR = 1.8

Brubaker S, Bukusi EA, Odoyo J, Achando J, Okumu A, Cohen C: **Pregnancy and HIV transmission among HIV discordant couples in a clinical trial in Kisumu, Kenya**. *5th IAS Conference on HIV Pathogenesis, Treatment and Prevention: Cape Town, South Africa. WELBC105.* Slides

Pregnancy Doubles Serodiscordant HIV Transmission Risk

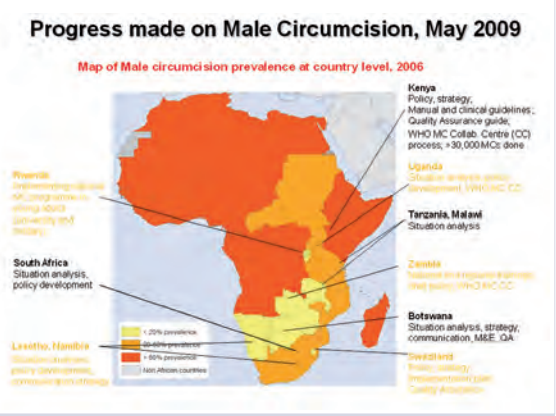
Pregnancy doubled the risk of HIV transmission in a two-year study of more than 500 HIV-discordant couples (one positive partner, one negative partner) in Kisumu, Kenya [34]. Sara Brubaker (University of California, San Francisco) found that, among 539 female partners (95% of them married), 189 (35%) conceived. Forty-one of 539 uninfected partners (8%) became infected during the study. Among women who conceived or men whose partner conceived, 10.8% became infected during follow up, compared with 5.9% of partners who did not have a child. Those rates translated into a 1.8 times higher risk of HIV infection in couples who had a child ($P=0.046$). About 30% of new HIV infections happened six months before conception, another 35% six months after conception, and the remaining 35% more than six months from conception.

Circumcision and HIV Risk in Female Partners

Three randomized trials conclusively demonstrate that circumcision lowers risk of HIV acquisition in heterosexual men [35-37]. But how the procedure affects HIV risk in female partners remains unknown. Two studies of serodiscordant couples – one was presented at IAS 2009 – could not establish that circumcision protects female partners from HIV.

A prospective observational study weighed the risk of HIV transmission in 1,096 serodiscordant couples, in which the male partner was HIV positive, who were enrolled in a trial of acyclovir to prevent HIV transmission [38]. During one to two years of follow up at 14 sites across Africa, 64 female partners became infected; viral sequencing established the male partner as the source in 50 of these women. One-third of the men were circumcised. Jared Baeten (University of Washington, Seattle) found that the overall new infection

Although circumcision lowered the risk of HIV acquisition in heterosexual men in three randomized trials [33-35] and is being adopted throughout Africa, research presented at IAS 2009 [36] and elsewhere [37] found no evidence that male circumcision prevents HIV transmission to female sex partners.



Slide from Track D Lead Rapporteur Sinead Delany-Moretlwe to illustrate circumcision discussion in Track C.

rate was 2.7 per 100 person years in female partners of circumcised men versus 4.4 in partners of uncircumcised men. Among newly infected female partners whose HIV sequence matched that of their partner, HIV incidence was 2.0 in partners of circumcised men and 3.5 in partners of uncircumcised men. In both of these comparisons, the risk of HIV infection adjusted for male viral load fell short of statistical significance (P=0.13).

A trial that randomized HIV-infected Ugandan men to immediate or deferred circumcision found no significant difference in HIV incidence among partners of circumcised men (18%) and uncircumcised men (12%) [39]. The investigators note that their analysis cannot exclude "the possibility of higher risk of transmission in couples who resumed sexual intercourse before complete [circumcision] wound healing".

Daily Acyclovir and Risk of HIV Transmission or Progression

Two previously published placebo-controlled trials of daily acyclovir found that this antiherpes drug does not prevent HIV acquisition in women and men infected with herpes simplex virus type 2 (HSV-2) [40,41]. A trial presented at IAS 2009 found that daily acyclovir does not prevent HIV transmission from HIV/HSV-2 infected people to their partners [42]. This trial, involving 3,408 heterosexual HIV-discordant African couples at 14 sites, randomized HIV-1/HSV-2 coinfected partners to placebo or to 400mg of acyclovir twice daily. Two-thirds of coinfected partners were female, no one was taking antiretrovirals, and participants reported taking 96.5% of acyclovir doses. Connie Celum (University of Washington, Seattle) reported that after 24 months of follow up, 84 new HIV-1 infections could be linked to study partners – 41 of them taking acyclovir and 43 taking placebo. Daily acyclovir significantly lowered the frequency of HSV-2-positive genital ulcers and cut HIV load by an average 0.25 log, but those benefits did not protect partners from HIV.

Although the modest decline in viral load recorded in this trial did not prevent coinfected partners from transmitting HIV to their partners, even a small decline may confer clinical benefits, according to results of another African study [43]. This placebo-controlled trial involved 2,284 women and 1,097 men coinfected with HIV-1 and HSV-2 but taking no antiretrovirals because they had a CD4 count above 250 cells/μL. Jairam R Lingappa (University of Washington, Seattle) found that 284 people taking acyclovir and 325 taking placebo reached a composite endpoint of CD4 counts below 200 cells/μL, ART initiation, or death from causes other than trauma. Those numbers translated into a 27% lower risk of reaching the composite endpoint (P=0.03).

Track C: Implications

The 3,000-woman analysis demonstrating lower rates of prematurity, abortion and stillbirth in women taking a triple-antiretroviral combination [32] adds to the already ample evidence supporting standard ART during pregnancy and breastfeeding. At this point, however, many pregnant or breastfeeding women do not receive standard ART because they do not meet national treatment criteria. In female Mombasa barmaids who reported transactional sex, starting ART coincided with less high-risk sexual behaviour [33], a finding suggesting that ART does not have a "sexual disinhibiting" effect, at least in this population. These results also confirm the feasibility of bringing high-risk women into care.

The study finding a higher risk of HIV transmission in HIV-discordant couples who have a child [34] indicates that discordant partners may continue to conceive even when they know one partner has HIV. If a portion of these pregnancies were intentional, the investigators suggest, these couples are risking HIV transmission in order to conceive. The results emphasize the importance of targeting serodiscordant married and unmarried couples in prevention initiatives.

Two studies failed to establish a lower risk of HIV infection in female partners of circumcised versus uncircumcised men [38,39]. The authors of the study presented at IAS 2009 suggest "short term interventions to protect against transmission risk during wound healing after circumcision of HIV-1 infected men could be considered, in order to realize

the longer term potential benefits of male circumcision" [38]. The authors of a previously published randomized trial add that protecting men from becoming infected by circumcising them probably lowers overall HIV transmission risk in a heterosexual population because it lowers the proportion of men carrying HIV [39]. There is no doubt that circumcision can be a valuable facet of HIV prevention for heterosexual men. (There have been no randomized trials of circumcision in men who have sex with men.)

The acyclovir trials show that this antiherpes agent has no role in preventing HIV transmission [42], but it can help slow HIV disease progression in people not taking ART [43]. The latter finding emphasizes the importance of testing simple, inexpensive non-ART strategies, such as acyclovir and cotrimoxazole, in people with HIV.

Track C lead rapporteur Sinead Delany-Moretlwe drew four lessons from prevention studies presented at the conference [30]:

- Treatment has progressed; prevention remains challenging.
- Biomedical interventions still require behavioural change; risk compensation needs to be monitored.
- The concept of treatment for prevention brings the treatment and prevention worlds closer than ever before.
- New interventions for prevention are most likely to be effective when delivered in combination.

HIV Investments Demonstrate Benefits for Other Diseases and Increased Uptake in Non-HIV-related Health Services

New evidence presented at IAS 2009 contributed much to the discussion of how the recent scale up of HIV treatment and care services has leveraged broader health benefits, particularly for women and children. New data also demonstrated that HIV scale up can help to reduce the prevalence and impact of other co-morbidities, such as TB and malaria. Examples of recent studies and conference abstracts that corroborate this key finding from IAS 2009 include:

- In Eastern Uganda, the increase in services for HIV/AIDS was accompanied by a reduction in non-HIV infant mortality of 83%, possibly due to the 90% reduction in children being orphaned.[1]
- In a rural region of the KwaZulu-Natal province in South Africa, following the introduction of infant ARV prophylaxis in 2001 and ART programmes in 2004, a 57% reduction in the under age-two child mortality rate was observed, showing a population-level effect of improved health services, particularly maternal ART and consequent survival.[2]
- In Haiti and Rwanda, Partners in Health documented increased use of non-HIV-related health services, including antenatal care, vaccinations and screening for sexually transmitted infections, as well as increases in the delivery of newborns in healthcare settings.[3]
- In most countries, coverage of key maternal and child health interventions has continued to improve at a steady pace with no clear evidence of a slow down since 2004.[4]
- Botswana had its first decline in infant mortality and increase in life expectancy in decades as the country focused on implementing HIV/AIDS programmes using both domestic and international resources.[5]
- A prospective Ugandan cohort study traced steeply declining malaria incidence after ART initiation, from 591 cases per 100 person years after one year to 476 cases after two years, 259 cases after three years, and 153 cases after four years.[6]
- A comparison of 2005 and 2008 TB and HIV rates in a well-defined South African township yielded strong evidence that wider ART accounts for a significant decline in TB prevalence [13]. Analyzing TB rates in 762 people surveyed in 2005 and 1,251 surveyed in 2008, Keren Middelkoop (University of Cape Town) found that TB prevalence fell by more than one-third, from 3% in 2005 to 1.8% in 2008, a significant decline in an analysis adjusted for age, gender, and HIV status.

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TRACK D: OPERATIONS RESEARCH

The new operations research track at IAS 2009 reflects a growing recognition of the need for applied research to inform the scale up of HIV programmes. The wide range and quality of presentations from a variety of disciplines exemplified one of the challenges for the conference: how to clearly define the operations research field in order to improve understanding of its role among investigators and other HIV professionals. In his summary report, Track D lead rapporteur George Schmid (WHO, Switzerland) defined operations research as research that "provides decision makers with information to improve the performance of their programmes... including identifying service delivery problems and evaluating a variety of delivery interventions" [44].

Key research presented in Track D included: programme evaluations; evaluations of various service delivery models; epidemiology; mathematical modelling; and cost-effectiveness studies. An IAS pre-conference workshop provided investigators with concrete information on how to use operations research methodologies to strengthen HIV prevention, care and treatment scale up. The need for new operations research to further build the evidence base for the health systems strengthening effects of HIV investments also dominated discussions at a two-day pre-conference meeting convened by the IAS.

First Drug Use and HIV Research Fellowships Awarded at IAS 2009

The IAS and the US National Institute on Drug Abuse (NIDA) awarded their first joint fellowships to Professor Maria Gudelia Rangel of Mexico and Kenya's Dr Michah Ongeri Oyaro.

NIDA and the IAS established the fellowship to advance the scientific understanding of the complex dynamics between drug use and HIV, while fostering multinational research on this linkage. This is the first year of the programme; it will continue to be offered every other year in conjunction with the IAS Conference on HIV Pathogenesis, Treatment and Prevention.

Dr Ongero Ovaro was awarded US$75,000 to undertake an 18-month post-doctoral training on social networks and molecular epidemiology of HIV, HBV and HCV infections among drug users in Kenya.

Professor Rangel will use the US$75,000 grant to extend her work into the field of substance use and HIV infection, and conduct research that could contribute to social public policy development in Baja California, Mexico.

Strategies for Strengthening Service Delivery

Several studies highlighted how task shifting and the decentralization of HIV services can leverage scarce health care resources to support scale-up efforts. Shabbar Jaffar (London School of Hygiene and Tropical Medicine) compared traditional facility-based delivery of ART with home-based care delivered by trained lay people (including medication provision, adherence support and referrals) in Uganda and found that both resulted in excellent and equivalent clinical outcomes based on mortality, CD4+ count and virologic response. While the cost of service provision was similar for both models, the home-based care intervention resulted in substantially reduced costs for patients [45].

Lipontso Makakole (Scott Hospital, Morija) presented encouraging results from a retrospective cohort analysis of a Lesotho programme that devolved routine patient management to nurses and referred patients coinfected with HIV and TB to specially trained counsellors. After two years, annual enrolment more than doubled, the proportion of adults presenting with less than 50 CD4 cells/μL was reduced from 27% to 13%, and 80% of patients were retained in care at 24 months [46]. Other presenters offered additional examples of strategies to expand health system capacity.

In Rwanda, Alphonse Kayinanga (Catholic Relief Services/AIDS Relief) and colleagues documented a programme that trained community volunteers to screen 3,340 HIV-positive individuals for TB, successfully referring 400 for clinical assessment [47]. Pius Tih (Cameroon Baptist Convention Health Board, Bamenda) described a public health programme in Cameroon that used trained health advisors to conduct contact tracing and partner notification for individuals testing positive in a high-prevalence region of the country [48].

Operations research also demonstrated how to better integrate service delivery among HIV programmes and among HIV and non-HIV health services. In his plenary presentation, Gerald Friedland (Yale School of Medicine, New Haven) described how an integrated HIV and TB treatment programme in KwaZulu-Natal – where more than 90% of TB cases are coinfected with HIV – not only resulted in substantially better clinical outcomes, but also uncovered the extent of multidrug- and extremely drug-resistent TB

prevalence and their effect on morbidity and mortality [49]. Friedland underscored a consistent theme: combinations of activities and approaches (for example, using a variety of interventions to reduce clinical and environmental factors that contribute to the spread of TB), rather than a single approach, are likely to yield the most benefit.

The importance of using a combination of approaches to deliver HIV and related health services was echoed in other Track D studies on service integration, including a study of Family Health International programmes in five African countries that assessed the extent to which reproductive health services were integrated into counselling and testing, and care and treatment programmes. The results suggest that, beyond condom provision, more work needs to be done to better integrate HIV with sexual and reproductive health services for women [50].

IAS President Julio Montaner addresses a Treatment Action Campaign rally before the start of IAS 2009.

Not all task-shifting interventions are created equal, however, as demonstrated by a Malawi study presented by Charity Kabondo (University of North Carolina Project, Lilongwe) in which trained traditional birth attendants (used by 44% of pregnant women) were used to expand the delivery of ARV prophylaxis to prevent vertical transmission. Although the use of traditional birth attendants expanded the use of ARV prophylaxis beyond traditional facility-based care, fewer than half of the pregnant women were identified as HIV positive and less than one quarter of infants diagnosed as HIV positive received nevirapine prophylaxis from traditional birth attendants [51].

Expanding ART Access and Retention

Yves Souteyrand (WHO, Geneva) presented encouraging data on increases in ART coverage in 2008, including an almost 50% one-year increase in coverage among children in sub-Saharan Africa [52]. Global ART coverage is currently estimated at 35% (45% for children younger than 15 years of age). However, evidence from a number of operations and clinical research studies demonstrates that earlier ART initiation for individuals with CD4+ counts below 350 cells/mm^3 results in substantial reductions in morbidity and mortality. Such evidence is expected to lead to changes in World Health Organization normative guidelines (anticipated to be released later this year), thereby making many more people treatment-eligible and reducing treatment coverage figures [53].

Against this backdrop, several studies addressed the vexing problem of ART programme retention. Kenneth Freedberg (Massachusetts General Hospital, Boston) presented a modelling and cost-effectiveness study of four lost-to-follow-up interventions (elimination of ART co-payments, provision of free opportunistic infection medications, increased health care worker training and coverage of transportation costs), which indicated that such interventions would be highly cost effective [54]. Based on five years of operations research, Anthony Harries from the IeDEA Collaboration identified 10 steps to improve access and retention, ranging from simple monitoring and evaluation activities to creative reward programmes for overstretched health care workers [55].

In an excellent overview of circumcision delivery in sub-Saharan Africa, Agot Kawango emphasized that while most countries have completed the necessary situation analyses and taken steps to develop political support and community messaging for circumcision rollout, health care worker shortages and health facility preparedness remain significant barriers to scale up. Encouragingly, she noted a number of

operations research studies underway aimed at evaluating several issues related to rollout, including safety, impact on sexual risk behaviours, HIV incidence and the comparisons of different intervention models, such as physician versus non-physician delivery. A study of circumcision implementation in Uganda, included in the Kawango overview, indicated no significant difference in adverse event rates by technique, health facility or cadre of health care worker [56].

In other prevention-related operations research, a promising modelling study on universal voluntary testing and treatment presented by Reuben Granich (WHO, Geneva) demonstrated the potential preventive effects of HAART at a population level [57]. Questions do remain on how this population-based approach could be made operational.

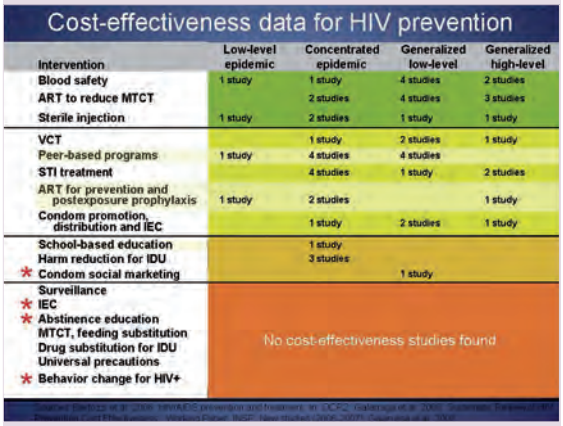
The Monitoring Debate: The Role of Laboratory Services

While there is consensus regarding the need for a baseline CD4+ count to guide initial clinical decisions, the frequency of subsequent CD4+ counts and the use of viral load monitoring was the subject of substantial debate at IAS 2009. Peter Mugyenyi (Joint Clinical Research Centre, Kampala) reported on final results from the five-year DART study, which compared clinical to laboratory monitoring using progression to WHO Stage 4 event or death as endpoints. There was no statistically significant difference between the two arms within the first two years and a small, but statistically significant difference from year three onwards, explained by slightly later switch rates in the clinical monitoring arm. Nevertheless, survival rate was excellent in both arms, at 87% and 90% for clinical and laboratory monitoring, respectively [58]. A cost-benefit analysis of the DART results indicated that laboratory monitoring for toxicity was expensive and provided no significant benefit, and that CD4+ monitoring may be cost effective as a targeted (rather than routine) strategy [59,60]. A modelling study presented by Sylvia Ojoo (University of Maryland/Institute for Human Virology, Nairobi) supported these data, suggesting that CD4+ count monitoring at six, 36 and 60 months was nearly as clinically effective as monitoring every six months and substantially more cost effective [61].

Financing and Cost Effectiveness: More and Better

A number of speakers referenced concerns regarding the potential impact of the global economic recession on HIV commitments from both government and private donors. In a provocative plenary presentation, Stefano Bertozzi (Instituto Nacional de Salud Publica, Mexico City) argued that while the HIV field has been successful in securing more money for AIDS in recent years, it has been less successful in getting "less AIDS for the money". He pointed out that few cost-effectiveness studies have been conducted on many common prevention interventions, and that too often, interventions are not chosen strategically or used where they will have maximum benefit [62]. Bertozzi called for strategies to improve the efficacy and cost effectiveness of current interventions, while advocating for additional investments to close the more than US$8 billion funding gap.

In his presentation, Financing the Long-Term Response to HIV, Stefano M Bertozzi, Mexico, pointed out that few cost-effectiveness studies have been conducted on many common prevention interventions, and that too often, interventions are not chosen strategically or used where they will have maximum benefit.



Bertozzi, S: **Financing the long-term response to HIV**. Plenary session (TUPL103). Slides

Paul Sax (Brigham and Women's Hospital/Harvard Medical School, Boston) presented the results of a cost-effectiveness analysis of ACTG 5164, a trial in which patients with opportunistic infections were randomized to receive either early or deferred ART [63]. The results are not necessarily generalizable to resource-limited settings. However, the finding is consistent with other studies demonstrating better clinical outcomes and reduced mortality when ART is initiated for everyone with less than 350 CD4+ cells, including the landmark Comprehensive International Program of Research on AIDS (CIPRA) HT001 study in Haiti. The Data Safety and Monitoring Board recently suspended CIPRA HT001 based on the significant interim differences between the deferred and early ART initiation arms [64].

Marielle Bemelmans (MSF, Brussels/Thyolo) presented a landmark cost-effectiveness study of the Médecins Sans Frontières-Ministry of Health ART programme in Malawi, demonstrating that a variety of measures, including task shifting, decentralization of care to health centres and community involvement, helped that country meet universal access targets (with 78% programme retention

by the end of 2007) while keeping the marginal cost of the ART programme to €2.6 per inhabitant per year, due to economies of scale [65].

Track D: Implications

There is some evidence that new operations research presented at IAS 2009 had an immediate impact on some policy makers in the conference's host country; a *Cape Times* newspaper article following the conference noted that the South African National AIDS Council would be meeting to discuss issuing guidance for earlier ART initiation, treatment for all infants diagnosed with HIV, and better integration of TB and HIV programmes [66]. Other notable evidence demonstrating how innovative service delivery models can successfully leverage community-based resources and lay workers to deliver HIV and public health interventions in the face of weak health infrastructure, health care worker shortages and entrenched HIV stigma is also likely to inform the continued rollout of HIV programmes.

IAS 2009 was a promising debut for the new operations research track. However, some important programme gaps remain. For example, the critical issues of drug and other medical commodity supply and procurement predictability and forecasting were barely touched on. In addition, the vast majority of data presented in this track related to vertical transmission and ART programmes (including health service integration), with substantially less attention given to prevention interventions beyond circumcision. This is in part due to the research focus of submitted abstracts, as well as the IAS conference's general focus on biomedical, rather than behavioural prevention interventions. However, without rigorous cost-effectiveness, modelling and programme evaluation studies to help identify the most effective prevention interventions, the evidence base for prevention will continue to lag behind that for care, treatment and support, and questions, such as those posed by Bertozzi about whether the HIV field is making the best use of its hard-won financing, will continue to be raised.

New Data on the Preventive Impact of Antiretroviral Therapy

IAS 2009 offered an overview of and several new insights on the potential role of antiretroviral therapy to prevent HIV transmission. In a plenary address, Reuben Granich (World Health Organization, Geneva) argued that the rationale for ART as a prevention strategy is irrefutable:[1]

- Transmission only occurs from persons with HIV.
- Viral load is the single greatest risk factor for HIV transmission.
- ART can lower viral load to undetectable levels.
- Prevention of vertical transmission is proof of the concept that ART reduces transmission.
- Observational evidence in heterosexual couples supports the concept.
- Previous modelling work suggests considerable potential.

Granich's own modelling study determined that treating all HIV-infected people with a CD4 count below 350 cells/mm3 would save 2.4 million lives between now and 2050, while universal voluntary testing and immediate ART would save 7.35 million lives.[2]

Other research on the preventive impact of ART yielded the following findings:

- A study of 2,993 HIV-discordant couples in Rwanda and Zambia recorded four HIV infections from partners on ART and 171 from partners not on ART (incidence 0.7% versus 3.4%).[3]
- A modelling study of male circumcision, condom use and ART in South Africa determined that 50% ART coverage would prevent 371,370 infections over 20 years, 75% coverage would prevent 635,790, and 90% coverage would prevent 770,330.[4] These prevention rates were greater than those attained with circumcision and less than those attained with condom use.

The conference provided a unique platform to bring together clinicians and prevention workers to discuss the implications of recent studies demonstrating the preventive impact of ART, further strengthening the links between prevention and treatment.

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Vuyiseka Dubula, Secretary General of South Africa's Treatment Action Campaign, addresses conference delegates.

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Ambassador Eric Goosby, U.S. Global AIDS Coordinator, discussed U.S. global health policy and the role of PEPFAR during a special session at IAS 2009.

IAS 2009 was organized by the International AIDS Society (IAS) in partnership with Dira Sengwe, a not-for-profit organization based in Pretoria, South Africa. The IAS is the world's leading independent association of HIV professionals, with 14,000 members in 190 countries working at all levels of the global response to HIV/AIDS. Dira Sengwe originated amongst a group of scientists and activists, who came together to help organize AIDS 2000 in order to bring attention to the plight of people living with HIV in Africa. Since 2003, Dira Sengwe has organized the South African AIDS Conference, one of the largest national AIDS conferences in the world.

Many thanks to the IAS 2009 Track Rapporteurs

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Jason Brenchley, USA
William Carr, South Africa
Luis Montaner, USA

Track B
Pablo Tebas, USA (Lead Rapporteur)
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Track C
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