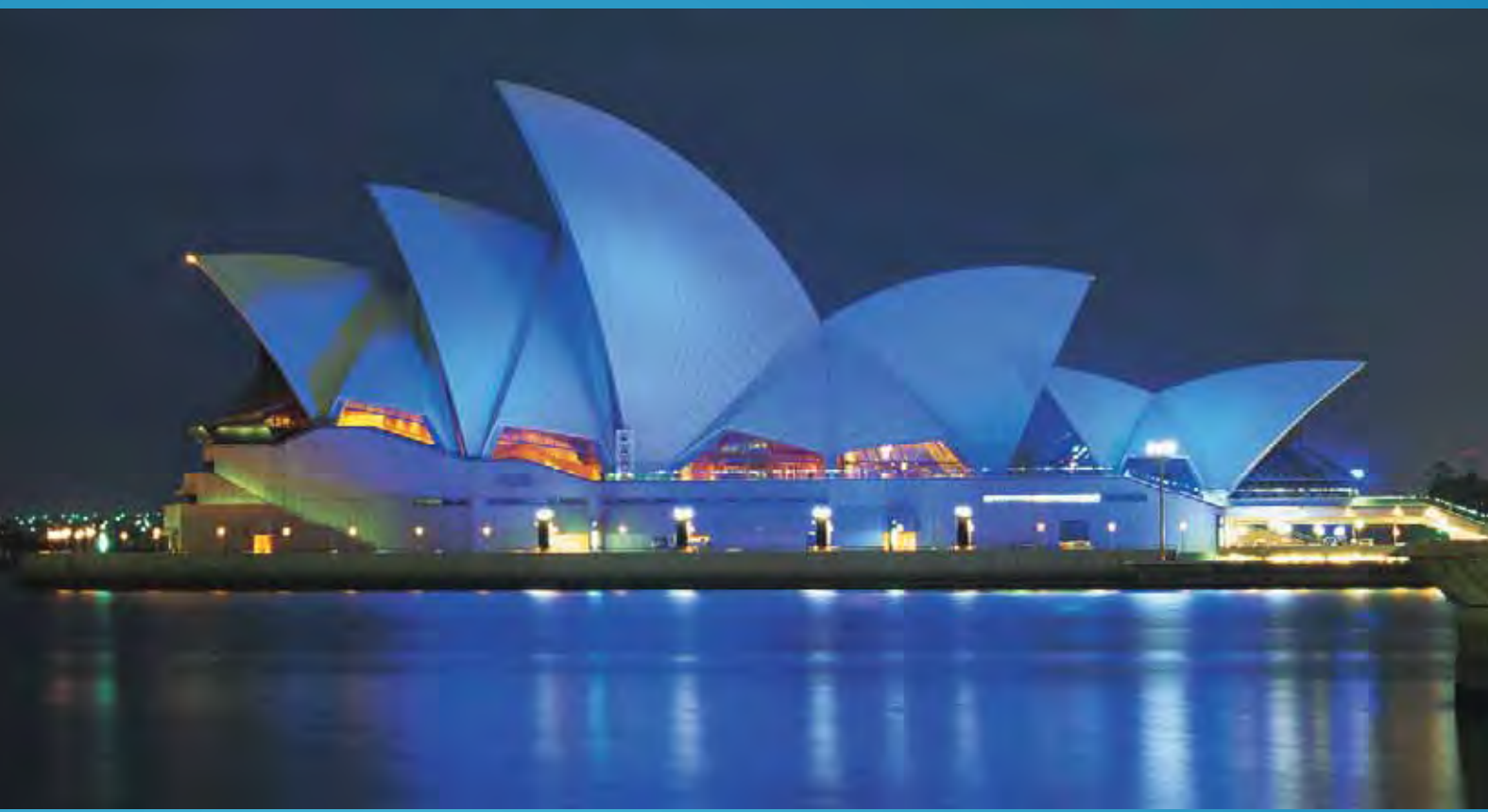
THE 4TH IAS CONFERENCE ON PATHOGENESIS, TREATMENT AND PREVENTION:

New Research and its Implications for Policy and Practice

IAS 2007 SYDNEY AUSTRALIA

International AIDS Society
Stronger Together



Content

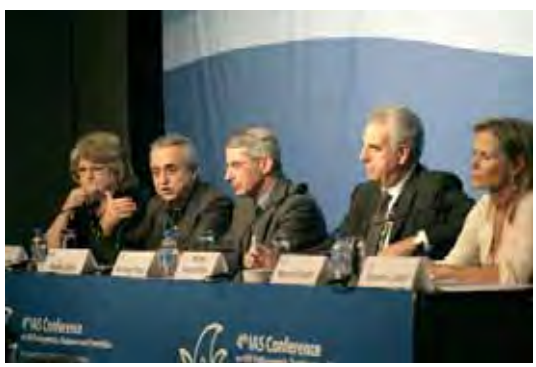
Introduction

Attendees at the 4th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2007) witnessed an array of new research in each of the three tracks during the 22-25 July 2007 meeting in Sydney, Australia. This report summarises key findings selected from the conference by a team of rapporteurs and analyses implications of these findings for further research as well as for policymakers and advocates.

Pedro Cahn, IAS President, opening session.

The abstract-driven programme emerged from stringent peer review of abstracts submitted by more than 3000 investigators from over 130 countries. Submissions for the Sydney conference represent more than a 50% jump from abstracts considered for the 2005 meeting in Rio de Janeiro. The United States, India, Nigeria, Australia, Uganda, Brazil, Nepal, Canada, Spain, and Italy sent the most abstracts to IAS 2007 reviewers. Abstract numbers are included, where relevant, in the text of this report, and a full abstract search of IAS 2007 and prior IAS conferences is available on the IAS website at **www.iasociety.org** or via the website of the electronic Journal of the International AIDS Society at **www.eJIAS.org**

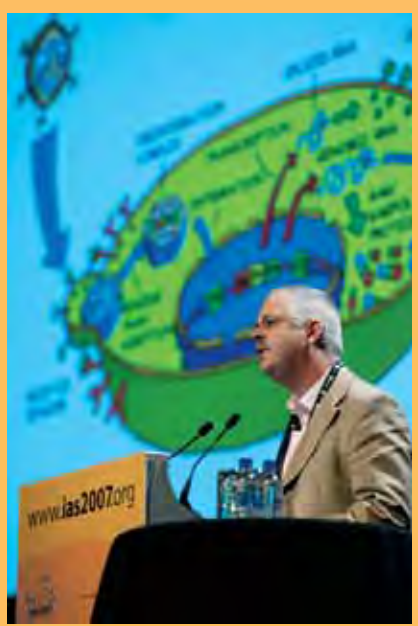
The previous IAS Conference on HIV Pathogenesis and Treatment in Rio, in 2005, saw the addition of biomedical prevention as a new pilot track to complement research on pathogenesis and treatment. IAS 2007 formally and permanently added prevention to the programme to acknowledge not only dramatic expansion of research in this critical field, but also to reflect the IAS commitment to an integrated approach to treatment and prevention.



From left to right: Levinia Crooks, Pedro Cahn, Anthony Fauci, Michel Kazatchkine and Sharon Lewin at the IAS 2007 opening press conference.

Track A: Basic Science

Gilda Tachedjian, BSc(Hons), PhD, from the Burnet Institute in Melbourne, highlighted important new data from basic research on HIV pathogenesis. She stressed that "basic research is critical for driving our understanding of how the virus reproduces in the cell, how it interacts with host cell factors, and how it subverts and damages the host innate and adaptive immune system." Bench research underpins all efforts to develop effective antiretrovirals, microbicides, and vaccines.



Ben Berkhout, Outpacing HIV: Viral fitness, escape routes and resistance patterns.

Resistance to microbicides and antiretrovirals

To infect T lymphocytes, HIV first binds to the CD4 receptor on the cell surface. CD4 brings the virus into contact with one of two coreceptors – CCR5 or CXCR4 – which facilitate viral-cell fusion. HIV that uses the CCR5 coreceptor is called CCR5 tropic (or R5 tropic), while virus that uses CXCR4 is termed CXCR4 tropic (or X4 tropic). R5 virus almost invariably establishes new infections and predominates in the early years of infection; X4 virus typically emerges in the latter stages of infection in about half of infected people.

Perhaps the most sobering basic research presented in Sydney came in a report identifying and characterising resistant virus selected by an anti-HIV microbicide, the first such result on record (WEBSS303). Researchers found that a single high dose of the CCR5 inhibitor PSC-RANTES applied vaginally in a macaque model allowed evolution of resistant virus that replicated as well as nonmutant (wild-type) virus.

Douglas Richman (TUBS101) and John Moore (TUBS102) reviewed new findings on resistance to CCR5 antagonists, including the discovery that HIV can bind to the drug-bound form of the CCR5 coreceptor as well as to the unbound form. Work unveiled in Sydney and elsewhere demonstrates that CXCR4-using virus that emerges in people taking CCR5 antagonists comes from pre-existing undetected pockets of X4 virus and not (so far) from treatment-induced mutations that force a coreceptor switch.

HIV can bind to the drug-bound form of the CCR5 coreceptor as well as to the unbound form.

Microbicides, mucosal immunity, and transmission

Understanding mucosal immunity and mechanisms of HIV transmission is a crucial prerequisite to developing microbicides that thwart sexual transmission of the retrovirus. Research presented in Sydney showed that fluorescently labeled viral particles can penetrate deep into intact squamous epithelia of the ectocervix and co-localise with CD4 cells in the lumen (MOPDA05). In short, this research demonstrates how HIV may interact with target cells in genital tissue to establish infection.

Using a panel of toll-like receptor ligands to stimulate human cervicovaginal tissue, other investigators demonstrated that novel endogenous antiviral factors can be induced in genital tissue (WEBS101 and MOPDA02). For example, ligands of toll-like receptors 3 and 4 induced proinflammatory responses, while two oligonucleotides – CpG B and C – inhibited viral replication in cervicovaginal tissue. These findings suggest that such factors may be effective mucosal adjuvants.

New drug targets and therapies

The conference offered extensive new data on new antiretrovirals, new drug targets, and new antiviral strategies. Several new agents, including the licensed protease inhibitor (PI) darunavir, foil viral replication by inhibiting protein-protein interactions, in addition to directly blocking the catalytic activity of HIV protease. Darunavir appears to alter protein-protein interactions by targeting the Gag-Pol embedded protease (MOPDX03), while a small molecule identified by in silico screening blocks interaction between the viral Tat protein and the host cell protein phosphatase-1 (MOPDX03).

Other work identified orally bioavailable fusion inhibitors with a mechanism distinct from the subcutaneously injected enfuvirtide (MOPDX01) and a novel class of reverse transcriptase inhibitors that bind to magnesium ions at the polymerase active site (MOPDX02). A novel Vpu ion channel inhibitor inhibits HIV replication in macrophages (MOPDX06). Bevirimat, a viral maturation inhibitor, is already in clinical trials. A conference study described a second-generation maturation inhibitor with less protein binding than bevirimat (MOPDX05).

John Rossi outlined a potentially exciting antiviral strategy involving a “triple-R vector” for HIV gene therapy (TUPL102). The vector attempts to sidestep resistance by expressing a combination of three types of RNA, including a small interfering RNA (siRNA) that targets viral RNA expressing Tat and Rev proteins. Stem cells or T cells transduced with this vector are reinfused into patients. The FDA has granted approval to test this strategy in clinical trials.

The conference offered extensive new data on new antiretrovirals, new drug targets, and new antiviral strategies.

Track A: Implications

Microbicide research: more in-depth research needed

Discovery that a vaginally applied microbicide can select resistant virus – and thus potentially render that microbicide ineffective – raises a question germane to researchers and advocates: Should candidate antimicrobials with different resistance profiles be considered for microbicide development versus agents that are used to treat HIV infections? These data also underscore the importance of developing microbicides containing a combination of agents with different modes of action to prevent the emergence of drug resistant strains. For policymakers and advocates, any finding on how one potential preventive strategy may fail underlines the importance of developing and integrating several preventive strategies.

Recent failure of two candidate microbicides (see Track C below) underscores the importance of understanding mucosal immunity and the mechanisms of HIV transmission.

Newer drug regimens for first line therapy?

The novel mechanism HIV deploys to escape CCR5 antagonists should invigorate basic research on the diverse resistance mechanisms the retrovirus can contrive. Any new work demonstrating HIV's remarkable capacity to escape drug pressure should inspire policymakers and advocates to press for second- and third-line regimens in developing countries, as well as for continued work on new agents with novel modes of action. Expansion of undetected X4-using virus in people beginning CCR5 inhibitors indicates the need to refine and deploy more sensitive assays to detect minority mutant populations.

For the research community the continuing abundance of new antiretroviral targets and strategies promises a vibrant research environment over the coming years.

For the research community the continuing abundance of new antiretroviral targets and strategies promises a vibrant research environment over the coming years. Investigators, and indeed drug developers, evince little fatigue in devising new anti-HIV tactics. Policymakers and advocates should consider these developments not merely as alternative strategies for patients from the developed world who have exhausted current treatment options, but as potentially more potent, less toxic, or more easily delivered therapies that may prove beneficial in countries with high HIV burdens in which antiretroviral programmes are currently being scaled up.

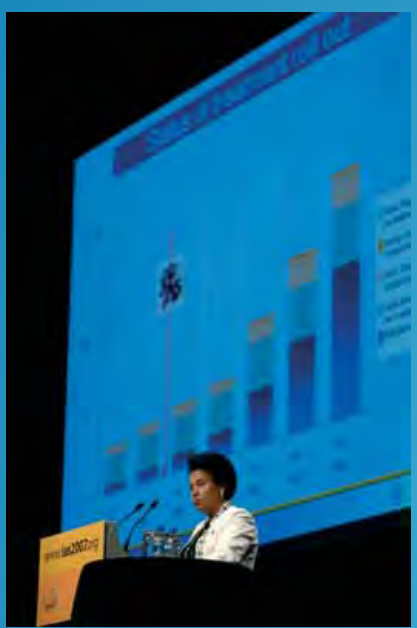
Key questions for scientists and policymakers

Tachedjian closed her presentation with a list of eight open questions of primary relevance to basic scientists. The final three questions also have obvious implications for policymakers and advocates because controlling viral evolution could limit the epidemic's diversity, clearing latent provirus could open the path to eradicating infection in individuals, and an antibody-stimulating vaccine – even if partially effective – could have a tremendous impact on HIV prevention.

1. Can immune activation be modulated to reduce viral pathogenesis?
2. Do new RNA-interference mechanisms provide realistic opportunities for HIV control?
3. Can we exploit host cell resistance factors to produce novel antivirals?
4. What are the correlates of effective immunity?
5. Are innate immune mechanisms adequate to control HIV?
6. Can we control viral evolution?
7. Can latent provirus be cleared?
8. Can we produce a vaccine that elicits neutralising antibodies?

Track B: Clinical Research, Treatment, and Care

Sean Emery, BSc, PhD, from the University of New South Wales in Sydney, analysed findings on new and current antiretrovirals in resource-limited settings and in developed countries, emphasising toxicities and the role of strategic clinical research informing clinical practice around the world.



Debrewerk Zewdie, Understanding the Task: ARV rollout and research issues in the developing world.

The researchers concluded that viral load testing can prevent misclassification of failure in resource-poor settings.

HIV/TB coinfection and ART failure

New data underlined two pivotal issues in the developing world: coinfection with mycobacterium tuberculosis and antiretroviral (ARV) treatment failure, particularly in the context of monitoring.
A pharmacokinetic study in Thailand found that most Thai patients can take 200 mg of nevirapine (versus 300 mg) twice daily with the antimycobacterial rifampin, although a 200-mg once-daily lead-in dose did increase the rate of suboptimal nevirapine levels (MOAB102). A study in Botswana detected low concentrations of anti-TB drugs in people with and without HIV infection, and low pyrazinamide concentrations correlated with poor outcome in people with AIDS (MOAB104). Research in Cambodia yielded evidence that simple whole blood interferon-gamma release assays may have a role in diagnosing TB immune reconstitution disease or incident disease (MOAB101).

Work in Malawi determined that immunologic and clinical definitions of ART failure in national guidelines misidentify approximately half of patients as failures and thereby often inappropriately call for second-line regimens (WEAB101). The researchers concluded that viral load testing can prevent misclassification of failure in resource-poor settings. Workers in Uganda confirmed that even experienced HIV clinicians can make inappropriate decisions to switch to second-line therapy in one third of cases (WEAB102). And research in Cambodia found that 2003 World Health Organization (WHO) criteria for treatment failure have low sensitivity in Cambodians (WEAB103).

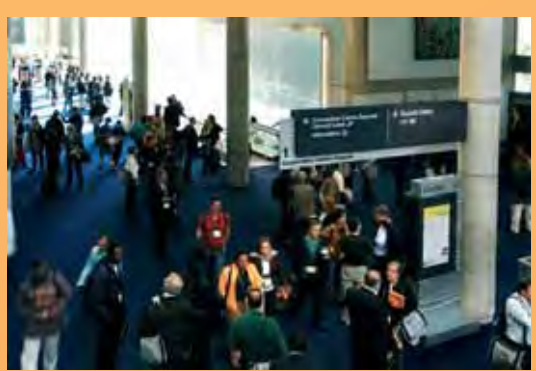
Argentine clinicians recorded a high rate of incident resistance to antiretrovirals among 40 children starting therapy with nonresistant virus (TUPEB054). After a median 5.5 months of follow-up, primary resistance mutations emerged in 28 children (70%). The clinicians attributed this high rate to poor adherence or poor drug bioavailability and called for studies of directly observed antiretroviral therapy in children.

Emery cited a comparison of nevirapine with abacavir (each with zidovudine/lamivudine) in 600 Ugandans with low CD4 counts (median 99 cells/µL) as among the most striking clinical reports at the conference (WEAB1LB). After 48 weeks of blinded follow-up, two standard response markers – viral load and CD4 change – favored the nevirapine regimen. But statisticians measured clear trends toward higher death rates, new WHO stage 4 events or death, and new WHO stage 3 or 4 events or death in the nevirapine group.

New drugs – new data

Extensive new data on recently approved antiretrovirals and those in late-and early-stage development were reported at IAS 2007. Two reports addressed the efficacy of combining the protease inhibitors (PIs) darunavir/ritonavir with the experimental nonnucleoside etravirine for people with multidrug-resistant virus (WESS204-1, WESS204-2), while another established the superiority of darunavir/ritonavir over lopinavir/ritonavir in treatment-experienced patients who had never tried those PIs (TUAB101).

Nearing licensing hearings, the integrase inhibitor raltegravir showed potent and sustained suppression of HIV in a direct comparison with efavirenz (TUAB104). The novel agent also proved safe and well tolerated. Whether faster viral decay with raltegravir than with efavirenz has any clinical significance remains to be seen (TUAB103).



Five presentations detailed trial results involving three CCR5 inhibitors: maraviroc (WESS104, WEPEB115LB, WEPEB116LB), vicriviroc (TUAB102), and INCB009471 (TUAB106). Maraviroc, on the verge of approval in the US and Europe during the conference, proved equivalent to efavirenz after 48 weeks in a 400-RNA copy comparison, but in a stringent analysis it lagged efavirenz in suppressing viral load below 50 copies/mL (WESS104). Vicriviroc plus other antiretrovirals stopped viral replication for 48 weeks in about one third of heavily pretreated patients. This trial charted a 12% rate of coreceptor switching among patients taking vicriviroc, and the meaning of new cancer diagnoses in 10 people taking vicriviroc remains unexplained. INCB009471, another CCR5 antagonist, has such a long half-life that less than once-daily dosing may be studied. PRO 140, a CCR5 monoclonal antibody, may be active against virus resistant to small-molecule CCR5 inhibitors like maraviroc, probably because the monoclonal antibody and small-molecule inhibitors bind differently to CCR5 (WESS201).

Antiretroviral toxicity

Four presentations detailed work on HLA-B*5701, a genetic polymorphism in the human leukocyte antigen system that signals abacavir hypersensitivity reaction (WESS101, WEAB305, WEAB306, WEPEB113LB). The central study in this cluster, the randomised PREDICT-1 trial, established the 100% accuracy of HLA-B*5701 screening in predicting immunologically confirmed hypersensitivity reaction.

The BICOMBO trial confirmed the value of switching nucleosides to a once-daily fixed-dose combination, either Truvada (tenofovir/emtricitabine) or Kivexa (lamivudine/abacavir), in virologically suppressed patients (WESS102). While no one switching to Truvada had virologic failure in 48 weeks, 4 (2.4%) switching to Kivexa did. Although this difference attained statistical significance, the finding that some patients inappropriately stopped Kivexa early because of presumed abacavir hypersensitivity (and thus counted as failures) clouds the clinical importance of that conclusion.

Strategies: when to start antiretroviral therapy

CHER study investigators reported critical interim results from this trial of immediate versus deferred antiretroviral therapy for 6- to 12-week-old infants in South Africa (WESS103). An independent review panel closed the deferred arm when the risk of death proved 76% lower in immediately treated children.

Emery noted that the when-to-start question remains more vexed for adults. Emergence of regimens more potent, simpler, and less toxic than those used a decade ago encouraged investigators to refocus on whether starting antiretrovirals earlier pays clinical dividends. Emery cited numerous studies offering evidence supporting at least continued evaluation of earlier treatment, including clinical findings (MOPL103, MOSY205, WEPEB030), cohort and biomarker data (MOSY202, WEAB301, WEAB302, WEPEB119LB), public health results (MOSY204), and immunologic data (MOPL102, MOBS201, MOSY201).

SMART trial investigators offered data suggesting a little-noted marker, d-dimer, may help arbitrate the when-to-start debate (MOSY202). In the SMART trial a striking finding was the large number of non-AIDS defining illnesses that occurred in patients with reasonably high CD4+ cell counts who had CD4+ guided periods in which they did not take antiretroviral therapy – thereby suggesting that there were processes associated with morbidity and mortality other than immunodeficiency in patients not taking ART in that trial. D-dimer – a fibrin degradation product – is a marker of ongoing activation of blood coagulation; SMART researchers assessed its levels in trial participants who interrupted or continued antiretroviral therapy. Their hypothesis was that HIV infection activates coagulation, so antiretroviral therapy should decrease coagulation and thus result in lower d-dimer levels. Indeed, d-dimer concentrations proved significantly higher in patients without antiretroviral experience when they entered the trial than in those who had taken antiretrovirals (0.69 versus 0.48 µg/mL (P = 0.02). Levels of the marker continued to rise significantly in the treatment-interruption group compared with the continuously treated group. Adjusted analysis determined that every 0.15 µg/mL higher d-dimer level raised the risk of major cardiovascular disease 12%, of death 23%, and of AIDS 40%.

Track B: Implications

Cited studies of HIV/TB coinfection underscore for policymakers and researchers the importance of planning for and managing these coincident epidemics in parallel. Policymakers should take special note of the studies questioning the validity of certain antiretroviral failure guidelines, while both clinicians and policymakers should weigh evidence that even experienced HIV clinicians err often in calling for second-line therapy. For policymakers, findings that immunologic and clinical definitions of treatment failure can be imprecise point to the likely value of developing and using practical and affordable laboratory tests in resource-poor settings.

Advocates must bear in mind that – although second-line drugs are surely essential in the developing world – the need for second-line regimens must be scrutinised objectively on a patient-by-patient basis. High rates of resistance recorded in Argentine children re-emphasise for all stakeholders that antiretroviral management is a complex undertaking that requires careful (and well-funded) laboratory monitoring to support prudent clinical follow-up.

Analysing the nevirapine-versus-abacavir trial in Uganda, rapporteur Emery suggested the discordance between markers of progression (RNA and CD4) and actual clinical outcomes implies that researchers, policymakers, and advocates can all learn lessons about (1) late use of antiretrovirals, (2) continued use of unacceptable regimens, and (3) inadequate monitoring in resource-limited settings.

Emery rated etravirine a “valuable, new, safe (nonnucleoside) option in the salvage setting” and darunavir/ritonavir a “credible option” when considering a ritonavir-boosted PI for experienced patients. Like others in the clinical arena, he remains impressed with findings on the integrase inhibitor raltegravir. Research on the two lead CCR5 antagonists showed, however, that hard-to-explain setbacks bedevil development of this class. New antiretrovirals cannot be embraced solely because of antiviral potency and novel mechanisms; they must also withstand exacting scrutiny of their safety.

The continuing proliferation of new antiretrovirals will force policymakers to decide how health insurance will pay for these often costly agents. For clinicians and investigators, the challenge becomes maintaining objectivity when appraising exciting novel compounds and keeping abreast of new findings to ensure proper use of these drugs if they are licensed.

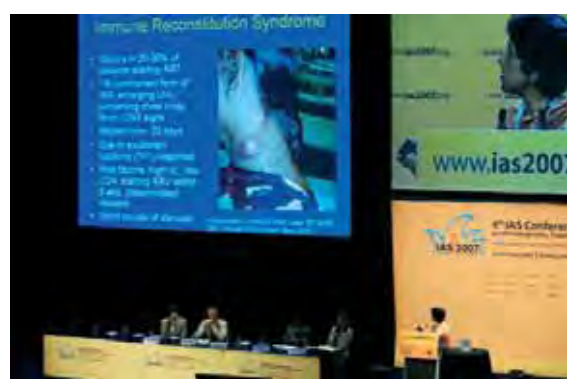
Committees reviewing newly approved drugs for possible inclusion in formularies of developing countries face pressure to assess the cost-benefit of these new drugs versus current agents. Although no IAS 2007 study addressed this specific issue, cost-benefit analyses from Brazil (TUPEB095) and Columbia (CDB495) showed that providing antiretrovirals drastically cut costs of HIV-related hospitalisation and other health care services, while researchers modeling the epidemic in British Columbia (MOPEA049) calculated that increasing the number of people on antiretroviral therapy from the current 50% to 75%, 90%, and 100% could prevent 3108, 4776, and 5701 new infections in the province over the next 25 years.

In establishing the value of genetic screening for toxicity to a single drug, the PREDICT-1 trial presents a daunting challenge to policymakers who must decide whether such screening should be instituted for all patients and – if it is – who will pay. Validation of a rapid flow-cytometric screening test (WEPEB113LB) may lower costs and speed results for some patients. Discovery of this genetic link and the well-planned testing of its use in clinical practice offer clinical investigators a model of toxicity research.

For clinical investigators, BICOMBO trial results underscore difficulties in planning and interpreting comparisons of two regimens in a rapidly evolving treatment environment. Had the trial incorporated HLA-B*5701 screening for abacavir hypersensitivity (instead of using it retrospectively), a small but perhaps critical number of participants may not have stopped abacavir for feared hypersensitivity and thus would not be counted as “failures.” Treatment advocates must ensure their constituencies are provided with fastidious and objective appraisals of such trial results in terms understandable to the layperson.

The rash of studies buttressing diverse rationales for treating HIV infection earlier in the course of disease should reinforce the appreciation by policymakers and advocates that well-considered principles of antiretroviral therapy are apt to shift regularly if drug discovery – and basic HIV research – continue at their current breakneck pace. A move toward earlier treatment in the developed world is bound to encourage all stakeholders to insist on strict and ongoing review of current treatment guidelines in developing countries.

This may prove especially true when reassessing paediatric HIV intervention guidelines, in light of early results from the CHER trial, which Emery characterised as “strategic in nature by design, properly conducted, and having an immediate impact upon treatment guidelines based on strong endpoints that affect practice, policy, and further research.”



Soumya Swaminathan, Antiretroviral therapy and TB: challenges in the clinic.

Track C: Biomedical Prevention

Lisa Maher, MA, PhD, from the University of New South Wales in Sydney, reviewed a host of prevention strategies, ranging from currently used and effective tactics (such as prevention of mother-to-child transmission and needle exchange), to effective methods waiting to be ramped up (male circumcision), to still-unproven interventions (microbicides, diaphragms, and HIV vaccines). Maher reminded colleagues of the need to deploy a suite of evidence-based interventions, stressing the interdependence of social and biomedical tactics. She underlined the dictum that efficacy in clinical trials does not automatically mean effectiveness in practice.

Promise Mthembu, a PLWHA perspective on HIV testing.

Microbicides and other female-controlled strategies

Two phase 3 placebo-controlled trials of cellulose sulfate gel, a vaginal microbicide, ended when results indicated that the gel may have increased the risk of HIV infection compared with placebo (WESS301, WESS302). The possibly heightened risk in the microbicide group was not statistically significant when final data were analysed. In-depth interviews with 104 women enrolled in a trial of MDP301 vaginal microbicide in Tanzania found that education resulted in good comprehension of the study concept and design, as well as awareness that efficacy of the microbicide would not be known until the trial concluded (MOAC303). As noted in the track A review, lab work identified specific mutations in the V3 loop and gp41 domains of HIV env selected in macaques vaginally treated with the CCR5 inhibitor microbicide PSC-RANTES and then exposed to HIV-1 (WESS303).

A strategy combining diaphragms, lubricant gel, and condom advice proved no better than condom advice alone in preventing HIV transmission (WESS304). Retention in this randomised phase 3 South African trial exceeded 90% in both study arms over 12 to 24 months, thanks to detailed locator information, extended clinic hours, and free transport and child care (TUAC105).

Scaling up circumcision programmes

A plenary address by Robert Bailey detailed results of three randomised trials that found a strong protective effect for heterosexual men who were circumcised (TUPL101). Maher noted that debate on circumcision now involves implementation. A cost-benefit model indicated that rollout of circumcision will be expensive (WEAC105) but appears to be justified by favourable cost-effectiveness and large projected health benefits.

An observational study in Australian men who have sex with men (MSM) found no correlation between circumcision status and HIV seroconversion (WEAC103). Most HIV infections in MSM probably result from receptive anal intercourse, and circumcision did not protect them. But neither did circumcision protect men who practiced insertive anal intercourse. The investigators noted that the size of their cohort limited statistical for subgroup analyses.

Juan Guanira, Male circumcisions: The cutting edge of HIV prevention.

Fight for health care, poverty reduction, and microfinance programmes.

MSM in Andean countries, especially city dwellers, evinced high willingness to participate in a circumcision trial (WEAC102). Investigators proposed that this willingness, coupled with low circumcision rates, offers excellent opportunities to conduct future prevention trials.

Prevention of mother-to-child transmission

Two nonrandomised comparative trials, one in Rwanda (TUAX102) and one in Tanzania (TUAX101), found that triple antiretroviral therapy almost entirely prevents HIV transmission to infants during breastfeeding. In the Rwandan trial only 1 of 176 infants (0.6%) became infected during breastfeeding by treated mothers. Cumulative transmission at 6 months in the Tanzanian trial measured 5%. Both studies used nonnucleoside regimens and counseled women on exclusive breast feeding.

Other interventions

Streamlined counseling and rapid HIV testing at US Veterans Affairs clinics significantly boosted rates of testing and result receipt compared with current practice, without changing HIV knowledge or risk behavior (TUPDB07).

A placebo-controlled trial in Tanzania found that twice-daily acyclovir did not lower HIV incidence by suppressing HSV-2 (TUPEC011). But 26% of enrollees withdrew from the acyclovir arm, most of them because of pregnancy. Two large randomised trials of acyclovir are underway.

Opioid substitution with buprenorphine dramatically decreased injection risk behavior in Ukraine, and the programme had a high retention rate (MOAC204). Expanding needle exchange access, removing limits on numbers of syringes distributed, and decentralising services decreased borrowing and lending of injection equipment among injecting drug users in Vancouver (MOAC205).

Ongoing phase 2b trials involve vaccines that elicit cytotoxic T-lymphocyte responses but not neutralising antibodies. Maher noted that while such vaccines will not prevent HIV infection, they could have secondary benefits including slowing HIV progression, reducing transmission, increasing T-cell response durability, and delaying time to antiretroviral initiation (MOBS301-304).

Track C: Implications

Failure of vaginal microbicides in two trials and emergence of resistant virus in a third study redouble the challenge researchers face in devising an effective microbicide. Closer analysis of why cellulose sulfate failed and why resistant virus emerged could hold clues to identifying and testing effective agents. Failure of these studies and a diaphragm-plus-gel trial will require policymakers to develop a workable prevention package that does not immediately include female-controlled strategies. At the same time, failure to lower HIV incidence by suppressing HSV-2 with acyclovir raises questions about the relative merits of this tactic, pending results of ongoing trials.

Triple-trial proof that circumcision lowers risk of infection in heterosexual men places the ball in the policymakers' court since they now must struggle with allotting resources to this intervention and integrating it into prevention plans. Community advocates and governments must share the burden of educating men and women that circumcision does not offer complete protection, and that proven interventions like condom use should be reinforced. Researchers must follow up hints that circumcision may also protect women and mount prospective studies to determine whether it will help protect MSM.

The two trials verifying efficacy of triple antiretroviral therapy in preventing transmission during breastfeeding provide strong evidence for treatment advocates calling for faster antiretroviral access for pregnant and breast-feeding women. Lisa Maher noted that formula feeding can be more expensive than triple antiretrovirals and that breast feeding has clear health advantages for infants when HIV transmission risk is minimised. Policymakers planning antiretroviral access in resource-poor countries must now weigh these factors in setting treatment priorities. Several speakers noted that uptake of proven MTCT interventions remained low in many countries and that efforts must be redoubled to ensure clinical trial efficacy is translated into effective interventions post-trial.

Dawn Smith: What is the status of our preparation for PrEP implementation?

The successful Ukrainian study of opioid substitution adds to the mountain of data backing effective strategies to limit HIV transmission among IDUs. Maher stressed that injecting drug use drives the epidemic in many regions, yet harm-reduction interventions for IDUs generally garner feeble support. Policymakers must face up to this evidence, and advocates must marshal these data in continuing to press for such programmes.

Other speakers emphasised that legislative and cultural barriers must be addressed if existing and planned interventions are to prove effective. For example, Mauro Guarinieri noted that some countries report allocating funding for IDU "treatment" programmes but in fact violate the human rights of IDUs in implementing those programmes (TUSY303).

Finally, Maher cautioned trial planners and policymakers alike against "cherrypicking" by focusing on interventions they personally favor when others may be more effective. Her overall advice for advocates is to lobby for legislative change, increase community and peer involvement, and fight for health care, poverty reduction, and microfinance programmes.

Michel Kazatchkine and Judy Auerbach, The future of global financing of prevention treatment, care and research.

Policymakers and advocates are encouraged to promote the Sydney Declaration.

Conclusions

As each of the three rapporteurs suggested, IAS 2007 chronicled significant headway – as well as some setbacks – in all three areas addressed in the meeting title. Through on-the-spot analysis and review, the meeting succeeded in translating basic, clinical, and prevention science into practical strategies that call for policy planning and programme development.

Investigators, health workers, policymakers, and advocates who attended the meeting or watched its proceedings in the extensive online coverage via kaisernetwork.org or Clinical Care Options will come away with a clearer understanding of which successful strategies merit immediate implementation, which need further research, and often precisely where new studies should focus.

Because only sound research can define mechanisms of HIV pathogenesis, treatment, and prevention, policymakers and advocates are encouraged to promote the Sydney Declaration, released prior to IAS 2007 by conference organisers, which states that “10% of all resources dedicated to HIV programming should be used for research towards optimising interventions utilised and health outcomes achieved.” The full text of the Sydney Declaration is available at **www.iasociety.org**

Crucial areas of research – notably work on novel antiretrovirals and diverse prevention tactics – began to mature in the year or so before the Sydney conference. Many ongoing trials that address unanswered questions in these fields will conclude over the next two years.
A substantial portion of those studies will provide important material for the next two major IAS meetings: the August 2008 XVII International AIDS Conference in Mexico City and the July 2009 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention in Cape Town.

Annex 1: Antiretrovirals Currently Approved in Europe and the US or in Phase III Trials

Generic name	*Brand name*	*Other names*	*Approval status*
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS)			
Abacavir	Ziagen	ABC	Licensed
Didanosine	Videx	ddI	Licensed
Emtricitabine	Emtriva	FTC	Licensed
Lamivudine	Epivir	3TC	Licensed
Stavudine	Xerit	d4T	Licensed
Tenofovir	Viread	TDF	Licensed
Zidovudine	Retrovir	AZT, ZDV	Licensed
NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS)			
Delavirdine	Rescriptor	DLV	Licensed; rarely used
Efavirenz	Sustiva, Stocrin	EFV	Licensed
Etravirine	—	TMC125	Phase III trials
Nevirapine	Viramune	NVP	Licensed
PROTEASE INHIBITORS (PIS)			
Amprenavir	Agenerase	APV	Licensed, largely replaced by fosamprenavir
Atazanavir	Reyataz	ATV	Licensed
Darunavir	Prezista	TMC114	Licensed
Fosamprenavir	Lexiva	FPV	Licensed
Indinavir	Crixivan	IDV	Licensed
Lopinavir/ritonavir	Kaletra	LPV/RTV	Licensed
Nelfinavir	Viracept	NFV	Licensed
Ritonavir	Norvir	RTV	Licensed; mostly used in low doses to boost other PIs
Saquinavir	Invirase	SQV	Licensed
Tipranavir	Aptivus	TPV	Licensed
FUSION INHIBITORS			
Enfuvirtide	Fuzeon	T-20	Licensed
CCR5 INHIBITORS			
Maraviroc	Selzentry in US, Celsentri outside US	— —	Licensed in US, approval pending in Europe
Vicriviroc	—	—	Phase III trials
INTEGRASE INHIBITORS			
Elvitegravir	—	GS-9137	Phase II trials
Raltegravir	Isentress	MK-0518	Phase III trials
MATURATION INHIBITORS			
Bevirimat	—	PA-457	Phase II trials

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