



FACT SHEET: NEW RESEARCH FROM IAS 2007

This fact sheet highlights a number of important research developments featured in the IAS 2007 abstract and non-abstract driven programme. For a complete list of research presented at the conference, please refer to the online [Programme-at-a-Glance](#) and/or the CD-ROM distributed to delegates at registration, which includes the full text of all abstracts.

CLINICAL RESEARCH

Over the last two years striking improvements in antiretroviral therapy—especially for people in whom several regimens already failed—emerged as the leading advance in HIV treatment in high-income countries. In low- and middle-income countries, steady though difficult improvements in access to care remain the top treatment story.

New Antiretrovirals

Potent three- or four-drug regimens (highly active antiretroviral therapy, or HAART) typically consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a nonnucleoside RTI (NNRTI) or a protease inhibitor (PI) boosted by low-dose ritonavir. HIV resistance to one or all of these drug classes can emerge if the drugs are not taken as prescribed, or if a person's drug levels fall for any reason. Resulting widespread resistance in wealthy countries spurred research on two types of new antiretrovirals:

- 1. PIs and NNRTIs that control HIV resistant to other drugs in these two classes.** Two recently licensed PIs and two investigational NNRTIs fit into this category (see [Appendix 1](#) for a list of related research to be presented at IAS 2007).
- 2. Antiretrovirals in new classes, which control HIV resistant to the first three classes because they act by different mechanisms.** The four main new classes are fusion inhibitors, CCR5 antagonists, integrase inhibitors, and maturation inhibitors (see [Appendix 1](#)). [Fusion inhibitors and CCR5 antagonists stop HIV from entering CD4 cells; integrase inhibitors block integration of HIV's genetic material into CD4 cell DNA; maturation inhibitors block a late step in HIV's life cycle to prevent mature new viruses from developing inside CD4 cells.]

New antiretrovirals in each of these categories invariably work better when combined with at least one other antiretroviral against which HIV has not evolved resistance mutations. Although all of these agents were first studied for activity against resistant HIV, several of them may well become options for first-line therapy. Availability of several new drugs in these groups spurred revisions in HIV treatment guidelines, which now say the goal of rescue regimens for people with highly drug-resistant HIV should be to push the viral load below a detection limit of 50 HIV RNA copies/mL. At IAS 2007, Monday's Special Session will explore the implications of new clinical data on international treatment guidelines. On the same day, a Symposium will examine emerging questions regarding the effectiveness and feasibility of treating early HIV disease.

The unusually high volume of Late Breaker abstracts submitted in the Clinical Research, Treatment and Care track of the conference has resulted in two Track B Late Breaker Special Sessions scheduled to take place on Wednesday, 25 July; one at 1:00 pm and a second at 4:30 pm. The second session will include a presentation of 24-week results from the DUET-1 and -2 trials evaluating two new agents, etravirine and darunavir, in patients with heavy treatment experience (abstracts [WESS204:1](#) and [WESS204:2](#)).

Antiretroviral Access

Although large majorities of people who need antiretroviral therapy (ART) in low- and middle-income countries do not receive these drugs, antiretroviral access has improved steadily over the past few years. A 2005 United Nations General Assembly resolution set 2010 as the target year for universal antiretroviral access. UNAIDS reports that “the number of people on antiretroviral therapy in low- and middle-income countries nearly doubled in 2005 alone.” In sub-Saharan Africa more than a million people were getting ART by June 2006, a 10-fold increase since December 2003.

In the past few months Thailand and Brazil have made headlines by threatening to enforce compulsory licensing of key antiretrovirals such as lopinavir/ritonavir and efavirenz. Compulsory licensing allows a country to circumvent patents and produce or import generic versions of licensed, patented products if that country declares the drug necessary to meet a health emergency.

Research from several countries, beginning with Haiti, shows that community-based programmes can deliver ART effectively. An IAS 2007 report from Uganda demonstrates the viability of this approach in Africa ([abstract WEPEB050](#)).

Starting and Interrupting ART

Emergence of long-term side effects with ART in the late 1990s led many HIV clinicians to begin therapy later in the course of disease (at CD4 counts close to 200 cells/mm³) and to study structured treatment interruptions as a way to limit side effects. But recent research produced evidence supporting earlier ART (at CD4 counts at or above 350 cells/mm³) and questioning the safety of treatment interruptions. Most notably the SMART trial linked drug breaks to faster AIDS progression *and* more frequent non-AIDS problems like heart, liver, and kidney disease. Several telling reports at IAS 2007 add to this changing view of when to start ART, whether to suspend ART, and how ART affects progression of non-HIV related diseases (see [Appendix 2](#)).

BIOMEDICAL PREVENTION

Circumcision

The most important news on HIV prevention in the past half year came when two randomized trials in Kenya and Uganda confirmed an earlier South African study showing that male circumcision more than halves the risk of HIV infection in heterosexual men. Among the top circumcision reports at IAS 2007 is a modeling study calculating the need for substantial funding and experienced surgeons to enable rapid rollout of circumcision in 14 sub-Saharan countries ([abstract WEAC105](#)). Cost-effectiveness analysis supports such a rapid scale-up.

A study of post-coital penile cleansing in Uganda’s rural Rakai district found a *higher* risk of HIV infection in uncircumcised men who cleansed themselves after sex, a result suggesting that cleansing should not be promoted as an alternative to circumcision ([abstract WEAC1LB](#)).

Mother-to-Child Transmission (MTCT)

Short-course prophylaxis with one or more antiretrovirals has proved tremendously effective in preventing MTCT of HIV. Recent published research indicates that women who take single-dose nevirapine to prevent MTCT can usually safely start a nevirapine-based regimen six months later. After successful prophylaxis at delivery, women may still transmit HIV to their infants if they breastfeed. Two critical studies at IAS 2007 found a greatly reduced risk of MTCT during breastfeeding among mothers taking triple-drug ART ([abstracts TUAX101 and TUAX102](#)). A Botswana study estimated that the number of infant infections prevented by MTCT prophylaxis rose from 595 in 2002 to 3,675 in 2006 ([abstract TUPEC029](#)).

Microbicides

HIV prevention methods controlled by women, including microbicides and diaphragms, remain a hot-button research priority. Though such methods do not diminish the urgent need to advance women’s rights globally, these measures can play a key role in a comprehensive prevention package. [Appendix 3](#) outlines leading studies on these issues at IAS 2007,

including 24- to 48-week results of a trial testing a diaphragm plus lubricant gel in nearly 5,000 African women and data from a study in monkeys suggesting that microbicide use may promote evolution of resistant HIV.

Pre-exposure Prophylaxis (PrEP)

Regular dosing of one or more current antiretrovirals (PrEP) may prevent HIV infection in high-risk people. This tactic generated much controversy because of worries over cost, behavioural disinhibition, and long-term use of antiretrovirals by uninfected people. A just-published two-year study on daily tenofovir (TDF) in high-risk women in Ghana, Cameroon, and Nigeria found no more side effects with TDF than with placebo (Peterson L, et al. PLoS Clin Trials 2007;2(5):e27). Although HIV risk was two-thirds lower in women taking TDF than in those taking placebo, the difference did not reach statistical significance because premature closure of the Cameroon and Nigeria sites robbed the study of statistical power. A study at IAS 2007 demonstrates in a small sample (n=22) that serodiscordant couples could successfully conceive without HIV transmission, when viral loads are fully suppressed and the sero-negative partner receives timed PrEP. ([abstract MOPDC01](#)).

HIV/TB Co-infection

Controlling co-infection with HIV and *Mycobacterium tuberculosis* has assumed even greater urgency since discovery of extremely drug-resistant TB (XDR-TB) in Africa, Asia, and Eastern Europe. IAS 2007 examines the often fatal partnership between HIV and TB in numerous reports, including a study recording high mortality in co-infected children despite antiretroviral therapy ([abstract CDA050](#)) and a survey of more than 2,000 co-infected adults in whom treatment innovations lowered rates of death, drug toxicity, and immune reconstitution inflammatory syndrome (IRIS) ([abstract CDA039](#)). Beyond the abstract programme, the conference will feature two additional sessions on HIV/TB co-infection: a satellite, co-sponsored by the International AIDS Society, the World Health Organization and other groups (*HIV/TB Co-Infection: Meeting the Challenge*, on Sunday, 22 July, 12:30-14:30) and a symposium on Tuesday, 24 July (*HIV/TB: An Evolving Epidemic*, 16:30-18:00).

BASIC SCIENCE

HIV Vaccines

Developing an effective vaccine against HIV remains the grail of HIV research. Many experts expect it will be many years before a vaccine is found that prevents HIV infection as effectively as vaccines to prevent polio, influenza, and other viral infections. Such vaccines depend on stimulating antibodies (proteins) against the virus, but that is a daunting task with HIV because the virus mutates so readily. Now, more research focuses on devising a vaccine that helps delay disease progression if a vaccinated person does get infected with HIV. Such a vaccine would stimulate T-cell responses to HIV and may try to stimulate antibodies at the same time. [Appendix 4](#) lists IAS 2007 studies of salient vaccine research.

Other Abstract Findings

Comparing CD4-cell subsets in antiretroviral treated patients and people without HIV, US researchers found evidence that HIV infection mimics the natural aging of naïve CD4 cells and that antiretrovirals may not fully reverse this effect ([abstract MOAA1LB](#)). Those findings may hold particular import for the growing population of aging people with HIV infection.

A lab study at the Burnett Institute in Melbourne offered the first evidence that HIV recombination—the natural merging of two distinct HIV genomes—can be regulated by externally applied molecular means ([abstract MOAA2LB](#)). Development of agents that control recombination may suppress evolution of multidrug-resistant HIV and viral variants that escape immune control.

HIV Pathogenesis

The field of HIV pathogenesis has significantly advanced over the past number of years with our increasing understanding of how the virus and immune system interact in causing disease. One of the newest concepts that is emerging is providing a clearer explanation for CD4 T-cell loss. The mechanism for this appears to be linked to a generalized activation of the immune system following initial HIV infection especially in the gut. Infection of the gut leads to release of bacterial products into the circulation allowing activation of the immune system through innate immune sensors. The immune system then is regulated by T-cells that attempt to control this hyperactive state. Results of these and other related studies will be presented during Plenary Symposium and oral abstract sessions.

There have also been significant advances in our understanding of the immune response to HIV. This includes studies of the more primitive innate immune system that is comprised of cells called dendritic cells that are the sentinels strategically placed at mucosal surfaces. There have also been advances in studies of the adaptive immune system that include both cellular (T-cell) and humoral (antibody) responses. Many studies have been performed in both human and animal models and will provide critical basic insights into the development of future HIV therapies and vaccines. The results of these studies will be highlighted during a number of oral abstract sessions.

Appendix 1. Notable new antiretrovirals

Generic name (brand name)	Drug class	Approval status	Reports at IAS 2007
Darunavir (Prezista)	Protease inhibitor	Licensed	<i>Abstract TUAB101:</i> Darunavir superior to lopinavir in lopinavir-naïve patients who have tried other PIs <i>Abstract WESS204:1 and WESS204:2:</i> Darunavir plus etravirine are active in salvage combinations for treatment-experienced patients (DUET-1 and DUET-2)
Tipranavir (Aptivus)	Protease inhibitor	Licensed	<i>Abstract WEPEB037:</i> Week 8 response predicts week 48 responses to tipranavir/ritonavir <i>Abstract WEPEB045</i> (see below)
Etravirine (also called TMC125)	Nonnucleoside	Late-stage development (phase 3 trials)	<i>Abstract TUPEB033:</i> Low rates of resistance to etravirine detected among antiretroviral-experienced, etravirine-naïve individuals <i>Abstract WESS204:1 and WESS204:2:</i> Etravirine plus darunavir are active in salvage combinations for treatment-experienced patients (DUET-1 and DUET-2)
TMC278	Nonnucleoside	Mid-stage development (phase 2 trials)	<i>Abstract WEPEA105:</i> Neuropsychiatric side effects less common with TMC278 than with the NNRTI efavirenz <i>Abstract TUAB105:</i> Metabolic profile looks better with TMC278 than with the NNRTI efavirenz
Enfuvirtide (Fuzeon)	Fusion inhibitor	Licensed	<i>Abstract CDB251:</i> Reuse of enfuvirtide in salvage prolongs survival <i>Abstract WEPEB045:</i> Better outcome, same safety profile, with enfuvirtide as without in tipranavir trial
Maraviroc (Celsentri)	CCR5 antagonist	Late-stage development (phase 3 trials); approval pending	<i>Abstract WEPEB115LB:</i> Maraviroc proved most potent when combined with the fusion inhibitor enfuvirtide or the protease inhibitor lopinavir/ritonavir in treatment-experienced patients who had not used those drugs <i>Abstract WEPEB116LB:</i> Maraviroc worked better in a twice-daily dose than once daily in combined 24-week results of MOTIVATE 1 and 2 <i>Abstract WESS104:</i> The double-blind MERIT study compared maraviroc with efavirenz (each with Combivir) in previously untreated people for 48 weeks
Vicriviroc	CCR5 antagonist	Late-stage development (phase 3 trials)	<i>Abstract TUAB102:</i> 48-week efficacy and safety data from ACTG 5211; longest follow-up of CCR5 antagonist so far <i>Abstract WEPEA108:</i> 12-week safety results of VICTOR-E1 trial
Raltegravir (also called Isentress and MK-0518)	Integrase inhibitor	Late-stage development (phase 3 trials)	<i>Abstract TUAB104:</i> 48-week efficacy and safety trial comparing raltegravir to efavirenz in treatment-naïve people <i>Abstract TUAB103:</i> Raltegravir induces faster viral decay than efavirenz <i>Abstract TUPEB032:</i> (see below)
Elvitegravir (also called GS-9137)	Integrase inhibitor	Mid-stage development (phase 2 trials)	<i>Abstract TUPEB032:</i> Diminished response to raltegravir after elvitegravir use suggests cross-resistance
Bevirimat (also called PA-457)	Maturation inhibitor	Mid-stage development (phase 2 trials)	<i>Abstract WEPEA110:</i> Aggregate safety data from four short-term studies

Appendix 2. New findings on starting and interrupting antiretroviral therapy (ART)

Issues	Abstract No.	Site(s)	Key findings
When to start ART, non-HIV related diseases	WEPEB019	Europe, Canada, Australia	Deaths due to non-AIDS diagnoses have become more common in recent years. Starting ART earlier may have an impact on non-AIDS causes of death.
When to start ART	WEPEB080	US	Starting ART at CD4 counts above 350 cells/mm ³ may allow restoration of normal T-cell populations.
Non-HIV related diseases	MOPEB084	US	Non-AIDS cancers are being diagnosed more in people on ART with high CD4 counts. Strategies beyond ART are needed to prevent them.
Non-HIV related diseases	MOPEC006	US	Men taking ART more than 8 years did not have more coronary atherosclerosis than HIV-negative men with a similar heart risk profile.
Non-HIV related diseases	WEAB302	US	Effective ART improves endothelial function—a marker of heart disease—regardless of ART regimen or lipid effects.
Treatment interruptions, non-HIV related diseases	MOPEB100	International	People interrupting ART in the SMART trial had bacterial pneumonia more often than people on steady therapy. Pneumonia risk was higher at low CD4 counts.

Appendix 3. Key research on microbicides and barrier methods

Method	Abstract No.	Site(s)	Key findings
Diaphragm and lubricant gel	WESS304	South Africa and Zimbabwe	This randomized trial compared a latex diaphragm, a lubricant, and condom use with condom use alone in almost 5,000 HIV-negative sexually active women for 12 to 24 months.
Microbicides	WESS303	US lab study	A candidate vaginal microbicide, PSC-RANTES, promoted evolution of resistant virus after one application in monkeys infected with simian/HIV (SHIV).
Microbicides	WEPEA085	International	This systematic inventory of microbicide assays and model systems noted unproductive redundancies, potential synergies, major research gaps, and opportunities for standardization, strategic collaboration, and investment.
Microbicides	CDC007	International	In the past year the number of microbicides in clinical development dropped from 14 to 10. Three of these 10 are being assessed in ongoing effectiveness trials, the final development stage.
Microbicides	WEPEA080	US	This work screened existing drugs for their microbicidal potential and rated the globally available, safe, and cheap vaginal fungicide ciclopirox a candidate for a targeted clinical trial.

Appendix 4. Vaccine research at IAS 2007

Site	Abstract No.	Key findings
Russia	TUPEA077	Early results of a Russian trial that should end in mid-2008 found an antibody-stimulating vaccine safe and capable of inducing an HIV-specific immune response.
India	TUPEA075	A vaccine that aims to induce immune responses against HIV-1 subtype C documented robust subtype-specific and cross-subtype immune responses in a mouse study.
Australia	TUPEA072	A vaccine that elicited both neutralizing antibodies and CD4 T-cell responses controlled HIV replication during CD8-cell depletion in monkeys exposed to a hybrid simian-human immunodeficiency virus (SHIV).