CONFERENCE SUMMARY REPORT

ON THE 6TH IAS CONFERENCE ON HIV PATHOGENESIS, TREATMENT AND PREVENTION (IAS 2011): RESEARCH HIGHLIGHTS AND IMPLICATIONS FOR POLICY AND PRACTICE

IAS 2011

6th IAS CONFERENCE
ON HIV PATHOGENESIS,
TREATMENT AND PREVENTION

17-20 JULY 2011 – ROME, ITALY

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Auditorium della Musica welcomes IAS 2011 delegates

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INTRODUCTION

The 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011) drew almost 8,000 participants from 142 countries to Rome, Italy to discuss the latest in HIV basic (Track A), clinical (Track B), prevention (Track C) and operations and implementation research (Track D). For years global HIV stakeholders have debated the relative merits of pursuing research on HIV prevention versus HIV treatment. That debate reached a resounding conclusion at IAS 2011, where four landmark trials demonstrated definitively – with statistical significance – that treatment with antiretrovirals is prevention. This report provides highlights of research presented in the four conference tracks, beginning with groundbreaking studies in biomedical prevention research (Track C), followed by coverage of key studies in Tracks B, A and D. In addition to summarizing the highlights of the IAS 2011 programme, the report analyzes their implications for future research, policy and programming. Citations for each of the studies referenced in this report include hyperlinks to the relevant sessions on the IAS 2011 website, providing readers with an opportunity to review the original presentations in detail. The conference also provided an opportunity for advocates to call for required investments to translate scientific promise into real programmes. Significant activism focused on the failure of Italy to fulfil its outstanding financial pledge to the Global Fund to Fight AIDS, Tuberculosis and Malaria (€260 million from the 2007 replenishment) or to commit any new funding. That theme – of whether governments in both the developed and developing world will capitalize on hard-won scientific knowledge by making the strategic investments required to fulfil their potential – resonated throughout the conference and will continue to be a central concern to all those working in HIV.

The Rome Statement for an HIV Cure

In conjunction with IAS 2011, a group of organizations including the International AIDS Society, American Foundation for AIDS Research, Agence nationale de recherches sur le sida, Treatment Action Group, International Treatment Preparedness Coalition, US National Institutes of Health, Sidaction and European AIDS Treatment Group launched the Rome Statement, calling for an increase in research into an HIV cure. Under the auspices of the International AIDS Society, a group of internationally recognized scientists and stakeholders is guiding the development of a global scientific strategy: *Towards an HIV Cure*. The strategy, to be launched at the XIX International AIDS Conference in Washington, has three objectives:

- To recognize the importance of developing a safe, accessible and scalable HIV cure as a therapeutic and preventive strategy against HIV infection and to help control the AIDS epidemic.
- To commit to stimulating international and multidisciplinary research collaborations in the field of HIV cure research.
- To encourage other stakeholders, international leaders and organizations to contribute to accelerating HIV cure research through their own initiatives and/or by endorsing this statement and supporting the alliance that the Advisory Board is building.

Individuals and organizations can be added to the Rome Declaration at:
http://www.iasociety.org/Default.aspx?pageId=584

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Demonstrators protest at Italy's non payment into the Global Fund

EXECUTIVE SUMMARY

- Three placebo-controlled trials of pre-exposure prophylaxis (PrEP) with one or two antiretrovirals taken daily by HIV-negative sexually active adults found that the strategy reduces the risk of HIV acquisition by 70% to 90% in people who adhere to their ARV prophylaxis schedule.
- A large randomized controlled trial that enrolled HIV-discordant couples (one partner positive and one negative) determined that HIV-positive partners who started standard triple antiretroviral therapy immediately rather than waiting had a 96% lower risk of transmitting HIV.
- South African researchers presented the first evidence that rollout of medical male circumcision programmes in Africa can decrease the spread of HIV; among men 15 to 49 years of age, adjusted HIV prevalence was 55% lower in the 2010 group than in the 2007 group (immediately prior to rollout), and among men 14 to 34 years of age it was 76% lower in the 2010 group.
- In the search for broadly neutralizing antibodies that could be used in a vaccine, US scientists demonstrated that antibodies they identified protect against 50% of a panel of HIV-1 strains by targeting the V2 and V3 loops of the HIV-1 envelope, which vary little from strain to strain of HIV.
- Two separate multi-site studies in Africa demonstrated that combination antiretroviral therapy (cART) for women during pregnancy and after delivery reduced the risk of maternal death and raised the chances of their infants surviving HIV-free. The DREAM Programme study in Mozambique and Malawi involved 10,150 pregnant women seen from June 2002 through June 2010; in a retrospective analysis, cART decreased the risk of maternal death by 40%. The four-country PEARL study found that infants of mothers who received ARV prophylaxis to prevent vertical transmission had almost a 70% better chance of HIV-free survival to two years of age than infants of mothers who did not take antiretrovirals.
- Elvitegravir, a once-daily HIV integrase inhibitor, proved non-inferior to raltgravir, the only licensed integrase inhibitor, in antiretroviral-experienced patients taking either drug for 48 weeks. After randomizing 702 patients with ARV-resistant virus or at least six months of ARV experience, 59% of those randomized to elvitegaravir and 58% of those randomized to raltegravir were able to reach undetectable viral loads. These findings provide an important new therapeutic option in this class.
- Researchers in Melbourne, Australia assessed cultured CD4 cells exposed to HIV to determine whether the phosphoinositol 3 kinase (PI3K) signalling pathway allows efficient integration and nuclear localization of HIV within CD4+ cells; the results showed that P13K antagonists result in complete elimination of integrated viral DNA but in only a slight change in levels of DNA localized to the nucleus. These findings indicate that P13K signalling is critical to HIV integration in resting CD4 cells and point to potential therapeutic applications that block P13K signalling. A US study assessing the impact of IL-7 and IL-15 on proliferation and persistence of HIV in CD4 cells points to IL-15 therapy as a potential strategy to drain the latent HIV reservoir. Both of these studies show promise for interventions that address one of the key challenges to an HIV cure: how to eliminate persistent viremia in resting CD4+ cells that are impervious to conventional cART.
- A home-based HIV testing and counselling (HBT) programme in Suba District, Uganda used a family-based approach to offering HTC. The programme (which delivered home-based testing and counselling from 2007 – 2009) in a poor, rural district, arranged home-based visits in advance, testing 68,315 individuals (including 10,790 couples). Eighty-four percent of households accepted the home testing and counselling offer (which included a counselling session for family members); 60.3% of individual members in these households were first-time testers. HIV prevalence in this cohort was 10.5% (12.3% female; 8.2% male). The majority of those testing HIV-positive (66.1%) were unaware of their HIV status.
- Increasing uptake and retention in care continues to be a major challenge in resource-limited settings, both pre-ART and post-enrolment. The Tingathe Programme in Malawi used trained community health workers (CHWs) to address the enormous challenge of improving early paediatric diagnosis and treatment in a country with 100,000 infants and children living with HIV (most of them undiagnosed), PMTCT programme coverage of only 35% (with over 50% loss to follow-up) and 30,000 new infant infections each year. In the 2.5 years since the inception of Tingathe, 15,997 children were tested and 4,766 were diagnosed HIV-positive. Enrolment of children on ART increased from less than 50 to 2,425, with fewer than 5% lost to follow-up.

IAS 2011 at a Glance

7, 866 participants, including:

- 6,779 delegates
- 1,261 participants from Italy
- 218 scholarship recipients (26 community scholarship recipients)
- 337 media delegates
- 158 volunteers
- 3,552 abstracts submitted
- 50 sessions (23 non-abstract driven sessions, 27 abstract-driven sessions)
- 9 plenary presentations
- 39 exhibits
- 31 satellite meetings
- 6 scientific prizes and awards

TRACK A: BASIC SCIENCES

Steps Towards HIV Cure Strategies

Several innovative cell-based experiments and studies in people with HIV yielded results that could point the way to HIV eradication strategies that deserve testing in humans.

HIV establishes lifelong infection by integrating its genetic material (HIV DNA) into a person's CD4 cells. When those cells go into a resting state, integrated virus remains impervious to antiretrovirals. Researchers in Melbourne, Australia assessed cultured CD4 cells exposed to HIV to determine whether the phosphoinositol 3 kinase (PI3K) signalling pathway allows efficient integration and nuclear localization of the virus.[1] After incubating the resting CD4 cells with activators or leaving them unactivated, the investigators infected the cells with HIV in the presence or absence of agents that inhibit the PI3K pathway. These experiments showed that PI3K antagonists result in complete elimination of integrated viral DNA but in only a slight change in levels of DNA localized to the nucleus. Results indicate that PI3K signaling is critical to HIV integration in resting CD4 cells.

US scientists from three centres assessed the relative impact of two cytokines, interleukin 7 (IL-7) and IL-15, on survival and proliferation of CD4 cells collected from cART-treated people and exposed to antiretrovirals in cell culture.[2] They determined that both IL-7 and IL-15 induce proliferation, activation and survival of antiretroviral-exposed CD4 cells. While the two cytokines induced similar activation marker levels, IL-7 induced higher CD4-cell proliferation than IL-15. In contrast, IL-15 induced viral production from latently infected CD4 cells at a level 4-fold higher than IL-7 (**Figure 4**).

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Anthony Fauci, IAS 2011 Press Conference, *Treatment is Prevention, the Proof is Here*

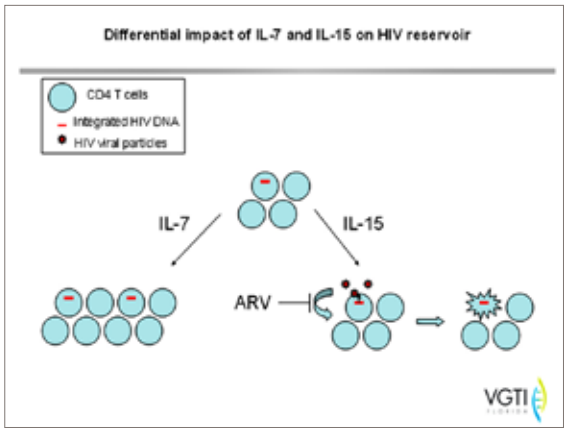

Figure 4. *Studies of CD4 cells collected from antiretroviral-treated patients showed that the cytokines IL-7 and IL-15 both induce proliferation, activation and survival of CD4 cells in the presence of antiretrovirals. IL-7 had a stronger impact on CD4-cell proliferation while IL-15 proved a stronger inducer of viral production from latently infected CD4 cells. (Slide courtesy of Claire Vandergeeten, abstract MOAA0101).*

Because HIV persists in fewer than 10% of memory CD4 cells, University of Montreal researchers aimed to identify markers of individual CD4-cell subsets that permit HIV infection.[3] They also sought to define the molecular mechanism of HIV permissiveness versus resistance in CD4 cells collected from people with HIV. CCR6, a receptor found on CD4 cells, is one candidate for promoting HIV permissiveness in CD4 cells, and CCR6-positive CD4 cells may infiltrate the gut via the gut-homing integrin β7. These experiments determined that CCR6-positive memory CD4 cells are highly permissive to HIV replication whether or not they also express integrin β7. These investigators also found evidence that CCR6-positive CD4 cells that express integrin β7 and CCR5 (another receptor) may be especially capable of disseminating HIV. All-trans retinoic acid (ATRA), the acid form of vitamin A, selectively enhanced permissiveness to HIV replication in CCR6-positive cells via CCR5 stimulation. The Montreal scientists concluded that CCR6 is a marker of memory CD4 cells imprinted with a transcriptional programme that favors HIV replication.

Antiretroviral-treated people with undetectable plasma viral loads have higher levels of inflammatory markers than people without HIV, a finding suggesting ongoing low-level viral activity. Because understanding causes of persistent inflammation in cART-treated people is important to preventing non-AIDS illnesses and to designing curative strategies, San Francisco researchers assessed the relationship between three measures of viral persistence and immune activation: (1) plasma HIV RNA (viral load), (2) cell-associated RNA and integrated proviral DNA and (3)

tissue-associated RNA and proviral DNA.[4] Specifically, the investigators wanted to examine associations between these measures and CD4 cells expressing PD-1, which reverses activation of CD4 cells. The study involved samples from 190 people in whom cART made HIV RNA undetectable in plasma.

The San Francisco team found modest positive correlations between cell-based measures of viral persistence and T-cell activation, but the low correlation values (rho 0.14 to 0.23) suggested other important factors contribute to this relationship. There was a highly significant positive correlation (rho 0.28, P = 0.0005) between proviral DNA levels in cells and frequency of PD-1-expressing CD4 cells, a finding consistent with PD-1 being a marker of latently infected CD4 cells. The researchers identified a strong correlation between viral persistence in gut-associated lymphoid tissue and CD4-cell activation (rho 0.65, P = 0.012). This study also showed that successfully treated patients with a CD4 count below 350 cells/mm^3 had higher measures of viral persistence and expansion of CD4 cells expressing PD-1 than did patients with higher CD4 counts.

A study in 435 HIV-positive Ugandan adults starting cART found that levels of tryptophan, an amino acid the body needs to synthesize protein, predicted both CD4-cell recovery and death.[5] Dietary protein builds tryptophan levels, but HIV infection induces tryptophan breakdown (catabolism). Researchers measured tryptophan levels in members of the Uganda AIDS Rural Treatment Outcomes cohort before they started cART and during treatment. Tryptophan levels rose during 12 months of antiretroviral-induced viral suppression. Lower pre-treatment tryptophan levels predicted diminished CD4-cell recovery after 12 months of suppressive cART, and higher pretreatment tryptophan catabolism and tryptophan catabolism during suppressive therapy predicted death. These correlations held true when the researchers accounted for self-reported dietary protein levels.

Implications of HIV Cure Research

In the two years before IAS 2011, a case report from Germany documented the first apparent cure of HIV infection.[6] Although the strategies that resulted in this cure (allogeneic bone marrow transplantation with stem cells from a donor carrying a gene that confers natural resistance to HIV infection) cannot be replicated on even a small scale, the result establishes the feasibility of ridding the body of HIV and providing an alternative to the need for lifelong cART.

Research presented at IAS 2011 suggested several avenues toward blocking establishment of latent HIV infection or activating latently infected cells and thus exposing HIV to antiretrovirals. The Australian cell study showing that HIV depends on the PI3K signalling pathway to integrate its genetic material into CD4 cells suggests that strategies targeting this pathway or the two proteins it yields (JNK and NF-κB) could lead to interventions that block establishment of latent HIV infection. The US study assessing the impact of IL-7 and IL-15 on proliferation and persistence of HIV in CD4 cells points to IL-15 therapy as a potential strategy to drain the latent HIV reservoir.

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Some of the IAS 2011 Scholarship Recipients

The Montreal cell study that identified the CCR6 receptor as a marker of memory CD4 cells highly permissive to HIV replication could help shape new therapeutic strategies that limit viral replication in memory cells without impairing their role in mucosal immunity.

The highly significant association between proviral DNA levels in cells of patients taking suppressive cART and frequency of PD-1-expressing CD4 cells[58] supports the rationale for a clinical trial of an anti-PD-1 monoclonal antibody aimed at clearing the latent viral reservoir. Such a study, AIDS Clinical Trials Group protocol 5301, is being planned. The higher measures of viral persistence and expansion of CD4 cells expressing PD-1 in patients with CD4 counts below 350 cells/mm^3 suggested to these researchers that curing such patients will be more difficult than curing patients with higher CD4 counts and may require unique interventions. These investigators argued that future studies of viral persistence should focus on cell- and tissue-based measurements of viral persistence, not on HIV RNA in plasma.

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Exhibition Area

A study in 435 Ugandans starting cART found that tryptophan levels predicted both CD4-cell recovery and death. IDO (indoleamine 2,3-dioxygenase) causes tryptophan breakdown in the body. Therefore these investigators proposed that interventions designed to block IDO induction could have a clinical impact in populations like this Ugandan group.

Together these findings confirm the central role basic research in identifying mechanisms of HIV pathogenesis and suggesting clinically relevant interventions that merit study. Four of the five studies summarized here involve viral eradication, a topic that continues to claim a pivotal place in the HIV research agenda.

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TRACK B: CLINICAL SCIENCES

cART for Pregnant Women/Mothers

In separate studies in Africa, combination antiretroviral therapy (cART) for women during pregnancy and after delivery reduced the risk of maternal death[1] and increased chances their infants would survive HIV-free[2] (**Figure 3**). The DREAM Programme has advocated cART during pregnancy and postpartum regardless of maternal CD4 count since 2002. A retrospective DREAM study in Mozambique and Malawi involved 10,150 pregnant women seen from June 2002 through June 2010, 8,168 of whom who started cART during prenatal care (group 1) and 1,982 of whom had already begun cART for their own health (group 2).[1] The women had a median CD4 count of 392 cells/mm^3, a median viral load of 3.9 $\log_{10}$ copies/mL (about 7900 copies/mL) and a median body mass index of 23.4 kg/m^2. There were 101 maternal deaths during pregnancy and up to six weeks after delivery to yield a maternal mortality of 0.99%.[1] Maternal mortality was 2.2% in women taking cART for fewer than 30 days before delivery and 0.6% in women taking cART for 90 or more days before delivery ($P < 0.001$). Multivariate analysis determined that longer cART duration lowered the risk of maternal death about 40% (OR 0.61, 95% CI 0.43 to 0.85). Higher initial CD4 count and higher body mass index were also associated with a lower risk of death. The impact of longer antenatal cART could be detected up to four years after delivery, even though many women stopped cART six months after delivery.

The four-country PEARL study found that infants of mothers who received antiretroviral prophylaxis to prevent vertical transmission had almost a 70% better chance of surviving HIV-free to two years of age than infants of mothers who did not take antiretrovirals.[2] Children whose mothers took cART or two antiretrovirals to prevent transmission had the best survival rate. PEARL involved 7,667 randomly selected mother-infant pairs in Cameroon, Côte d'Ivoire, South Africa and Zambia in which the infant was two years old or younger. Among all infants, 1,002 (13%) had been perinatally exposed to HIV, 844 (11%) had a negative HIV DNA test, 105 (1.4%) had a positive test and 53 (0.7%) had died. Infants whose mothers took antiretrovirals to prevent vertical HIV transmission had a 67% higher chance of HIV-free survival at two years (adjusted hazard ratio 1.67, 95% CI 1.05 to 2.65). Survival rates were 88.2% with cART, 88.5% with nevirapine plus zidovudine, 82.9% with nevirapine alone and 78.3% with no antiretrovirals.

Starting cART in Children

In a result at odds with studies of adults and children under one year old,[3] researchers in Thailand and Cambodia found no advantage in progression to AIDS or death when starting cART immediately in one to 12 year-old children with moderately advanced HIV infection.[4] The surprising results require further analysis and confirmation in other pediatric populations.

The PREDICT study involved 300 children who had not started cART and had a CD4 of between 15% and 24%.[4] (WHO recommends starting cART in all children up to two years regardless of CD4 percent and in any two to 5 year-old with a CD4 count below 750 cells/mm^3 or a CD4 percent below 25%.[5]) Researchers randomized children to start cART immediately or to wait until their CD4 fell below 15% or they developed CDC category C AIDS. Children's age averaged 6.4 (+/-2.9 standard deviation), so few participants were under three years old. All children had their CD4 cells measured every 3 months. After 144 weeks of follow-up, the treatment groups did not differ substantially in the two primary endpoints: AIDS-free survival (97.9% in the immediate-cART group and 98.7% in the deferred group) or neurodevelopment as measured by the Berry score (84.7 immediate and 86.8 deferred). Nor did the groups differ significantly in rates of CDC category B or C events, deaths, hospitalizations, or grade 3 or 4 adverse events. The deferred-cART group had significantly higher rates of newly diagnosed thrombocytopenia (10 versus 1, $P = 0.03$) and herpes zoster (13 versus 2, $P = 0.03$). Growth measured by height-for-age Z score and weight-for-age Z score was better in the immediate group. See the Implications section below for further discussion of these findings.

Comparing WHO-Recommended TDF Combinations

A systematic review of 29 studies evaluating four WHO-recommended tenofovir (TDF)-containing first-line regimens found that one of them – TDF plus lamivudine (3TC) and nevirapine (NVP) – proved inferior to comparison regimens and led to high rates of virologic failure and resistance.[6] WHO recommends four TDF-containing regimens for first-line therapy in adults and adolescents, TDF/3TC/NVP, TDF/emtricitabine (FTC)/NVP, TDF/3TC/efavirenz (EFV) and TDF/FTC/EFV.[7] To assess efficacy of those four combinations, researchers reviewed 29 prospective and retrospective studies. Three regimens – TDF/FTC/NVP, TDF/3TC/EFV and TDF/FTC/EFV – consistently proved equivalent or superior to comparison regimens. But TDF/3TC/NVP was inferior to zidovudine/3TC/NVP in two of three studies, with failure rates of 29% versus 3% and 21% versus 10%. In the third

study, which had no comparison arm, 30% of people taking TDF/3TC/NVP had virologic failure. The TDF-related K65R mutation arose in 44%, 40% and 34% of patients in whom TDF/3TC/NVP failed in those three studies, This combination is the least well-studied of the four.

Randomized Switch From ABC/3TC to TDF/FTC

In a randomized 48-week trial, switching from a stable regimen containing abacavir (ABC) and 3TC to TDF/FTC reduced the risk of virologic failure.[8] US researchers mounted this study because earlier research indicated a higher virologic failure rate with regimens containing ABC/3TC versus TDF/FTC.[9,10,11] The 311 study participants had a viral load below 200 copies/mL for at least 3 months while taking ABC/3TC plus a ritonavir-boosted protease inhibitor (PI). The investigators randomized them to continue ABC/3TC or switch to TDF/FTC while keeping the same PIs. After 48 weeks a noncompleter-equals-failure analysis determined that similar proportions maintained a viral load below 200 copies/mL: 83.3% on ABC/3TC and 86.5% on TDF/FTC. Defining virologic failure as a confirmed rebound above 200 copies/mL or a viral load above 200 copies/mL at the last study measurement, the researchers counted 11 virologic failures in the ABC/3TC group versus three in the TDF/FTC group ($P = 0.034$) by week 48. Most people with virologic failure in either group had low-level viremia at week 48 or regained viral suppression without switching antiretrovirals. Rates of grade 3 or 4 adverse events were similar with ABC/3TC (10%) and TDF/FTC (8%), but fasting lipids improved more in people switching to TDF/FTC. These results mean switching to TDF/FTC is noninferior to maintaining ABC/3TC.

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Serena Spudich, Late Breaker Cross Track Session

Two New Integrase Inhibitors: Elvitegravir and Dolutegravir

Elvitegravir, a once-daily HIV integrase inhibitor, proved noninferior to raltegravir, the only licensed integrase inhibitor, in antiretroviral-experienced patients taking either drug for 48 weeks.[12] The phase 3 trial involved 702 patients with antiretroviral-resistant virus or at least six months of anitretroviral experience. Researchers randomized them to raltegravir (400 mg twice daily) or elvitegravir (150 mg once daily, or 85 mg once daily with atazanavir or lopinavir). Everyone also took a fully active ritonavir-boosted PI plus one other drug chosen by the investigator. (Elvitegravir requires a boosting agent like ritonavir; raltegravir does not.) When the study began 63% of participants had virus resistant to two or more antiretroviral classes. An intention-to-treat analysis determined that 59% of those randomized to elvitegravir and 58% of those randomized to raltegravir had a viral load below 50 copies/mL at week 48. These results established that elvitegravir is noninferior to raltegravir in these patients. Among patients with virologic failure, integrase mutations developed in 27% taking elvitegravir and 21% taking raltegravir. Discontinuations because of adverse events were low in both study arms (2% with elvitegravir and 3% with raltegravir).

Dolutegravir, another investigational once-daily integrase inhibitor, controlled viral replication as well as the nonnucleoside reverse transcriptase inhibitor efavirenz through 48 weeks in a phase 2b trial that randomized 205 antiretroviral-naive patients to one of three dolutegravir doses or to standard-dose efavirenz.[13] Four patients discontinued treatment in the efavirenz arm because of adverse events (8%), compared with two patients (1%) randomized to dolutegravir.

Impact of early cART on HIV disease progression. HPTN 052, the international trial that randomized HIV-positive partners in HIV-discordant couples to immediate or delayed cART, found significantly slower HIV progression in people starting cART with a CD4 count above 350 cells/mm^3 rather than below 250 cells/mm^3. These findings are detailed in the first section of this report.

Implications of Clinical Research

Three studies presented at IAS 2011 found that treating HIV-positive pregnant women and new mothers with combination antiretroviral therapy (cART) offers clinical advantages to the mother and newborn compared with one- or two-drug antiretroviral prophylaxis (**Figure 3**).

These results mesh with those of the Mma Bana Study in Botswana, which found that cART during pregnancy through six months postpartum cut the vertical transmission rate to 1.1% in breastfeeding infants at that point (**Figure 3**).[14] WHO already endorses maternal cART for PMTCT regardless of the mother's CD4 count - as one of two PMTCT options.[15] In light of these new findings and results of HPTN 052 (reviewed in the first section of this report), WHO and national policymakers will have to decide whether to eliminate the other PMTCT option (maternal zidovudine plus infant antiretroviral prophylaxis) and rely on maternal cART. Access to maternal cART remains a limiting factor.

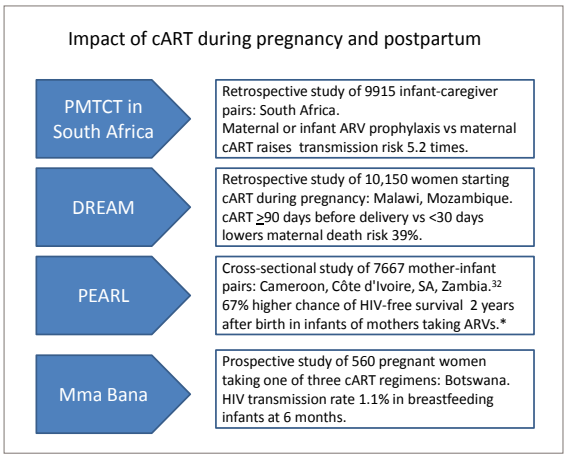

Figure 3. *These four studies - three of them reported at IAS 2011 - found substantial clinical advantages for mothers and infants when mothers took cART to prevent vertical transmission of HIV.*

The CHER trial provided definitive evidence that starting cART immediately for HIV-positive infants sharply lowers the risk of disease progression and death.[3] As a result WHO recommended cART for all HIV-positive children up to two years old regardless of CD4 count.[5] At IAS 2011, PREDICT trial investigators reported that immediate cART for 1 to 12 year-old children with a CD4 between 15% and 24% did not delay HIV disease progression or death.[4] This startling result from Thailand and Cambodia requires closer scrutiny before recommendations change or physicians consider delaying cART for children. Children in PREDICT had their CD4 percent measured every three months, an interval that probably cannot be matched in many clinics, and the investigators noted that the study group included only a small number of one to three year-old children so the findings may not apply to them. WHO recommends cART for two to five year-olds with a CD4 count at or below 750 cells/mm^3 or a CD4 percent at or below 25%, whichever is lower, regardless of WHO clinical stage.[5]

A systematic review evaluating WHO-recommended TDF-containing first-line combinations[37] found that one – TDF/3TC plus nevirapine – may be inferior to comparison regimens.[6] US antiretroviral experts do not list this combination as a preferred, alternative or acceptable initial regimen.[16] The investigators called for urgent study of this combination "before [it] is widely deployed for initial antiretroviral therapy".[6] While WHO and other policy-setting bodies decide whether to revise recommendations for this combination, clinicians must decide whether to favor one of the other three WHO-sanctioned TDF regimens.

The randomized trial comparing staying with an ABC/3TC combination or switching those nucleosides to TDF/FTC added new data on the choice between these critical regimen backbones.[8] Although the virologic failure rate was higher among patients maintaining ABC/3TC, most protocol-defined failures reflected low-level viremia, and the proportion of participants whose viral load stayed below 200 copies/mL was similar in the two treatment arms. US antiretroviral guidelines list TDF/FTC as the preferred first-line backbone, while ranking ABC/3TC as an alternative.[16] European guidelines recommend either of these coformulated pairings for initial treatment but stress that ABC/3TC cannot be used in HLA B*5701-positive people.[17] Three earlier trials documented a higher virologic failure rate with regimens containing ABC/3TC versus TDF/FTC,[9,10,11] and TDF/FTC has a better lipid profile than ABC/3TC.[8,18] On the other hand, numerous studies show an association between TDF and kidney dysfunction[19,20] or declining bone mineral density.[21,22] For example, analysis of 357 STEAL study participants found increased bone turnover and spine and hip bone mineral density loss with TDF/FTC versus ABC/3TC, although treatment groups did not differ in 10-year fracture risk or need for antiresorptive therapy.[22]

Two studies compared new integrase inhibitors – elvitegravir and dolutegravir – with raltegravir, the only licensed integrase inhibitor[12] or with efavirenz.[13] Continued development of antiretrovirals is essential because new agents may have differing toxicity, resistance and convenience profiles that make them a better choice for individual patients. Raltegravir requires twice-daily dosing, whereas elvitegravir and dolutegravir are once-a-day drugs. Elvitegravir requires a boosting agent, whereas raltegravir and dolutegravir do not, but elvitegravir will probably be co-formulated with cobicistat, a non-ritonavir booster, and researchers are working on a four-in-one once-daily agent that combines elvitegravir, cobicistat, TDF and FTC.[23] The developer of elvitegravir has also made all four of these agents available through a patent pool that should increase access to these important antiretrovirals at relatively low

cost.[24] More antiretroviral manufacturers are expected to join the patent pool; if that happens, antiretroviral access will continue to increase as more low-cost generics become available.

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IAS 2011 Delegates

TRACK C: PREVENTION SCIENCE (INCLUDING VACCINOLOGY)

Three PrEP Trial Results

Researchers at IAS 2011 presented data from the first two randomized trials to demonstrate that one- or two-drug PrEP greatly reduces the risk of HIV-negative sexually active heterosexual adults acquiring HIV (**Figure 1**).[1,2] An earlier trial, iPrEx (updated at IAS 2011), demonstrated the protective value of PrEP in men who have sex with men (MSM).[3]

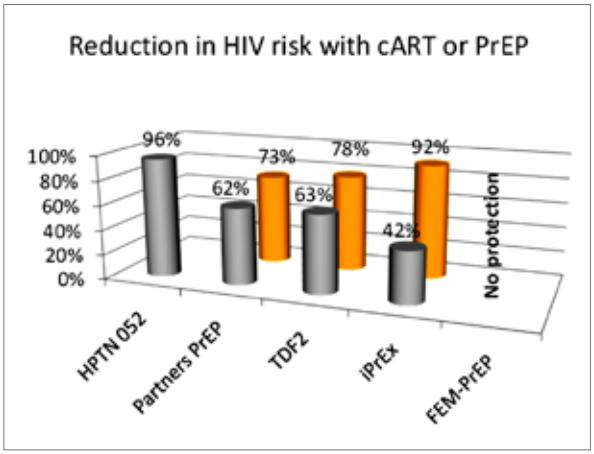

Figure 1. *Three trials of antiretroviral pre-exposure prophylaxis (PrEP) and one trial of immediate versus delayed combination antiretroviral therapy (cART) demonstrated that these strategies significantly lower the risk of HIV acquisition or transmission.*

For HPTN 052: *Immediate versus delayed cART.*
For Partners PrEP: *Front bar, TDF alone; back bar, TDF/FTC (both vs placebo).*
For TDF2: *Front bar, TDF/FTC; back bar, TDF/FTC with good adherence (both vs placebo).*
iPrEx: *Front bar, TDF/FTC; back bar, TDF/FTC with good adherence (both vs placebo).*
FEM-PrEP: *TDF/FTC vs placebo.*

Partners PrEP, the largest PrEP trial so far, randomized the HIV-negative partners from 4,758 HIV-discordant couples in Kenya and Uganda to once-daily tenofovir (TDF), once-daily TDF/emtricitabine (FTC), or placebo.[1] As in all PrEP trials discussed here, participants received a comprehensive package of HIV prevention counselling and services, and condom use was high. In July 2011, the Data Safety and Monitoring Board (DSMB) recommended closing the placebo arm and publicizing results because of strong advantages in the daily TDF and TDF/FTC arms. HIV incidence per 100 person-years was 0.74 with TDF alone, 0.53 with TDF/FTC and 1.92 with placebo. Daily TDF alone lowered HIV acquisition risk by 62% compared with placebo ($P = 0.0003$), while TDF/FTC reduced the risk 73% ($P < 0.0001$). The difference between TDF and TDF/FTC was not statistically significant ($P = 0.18$), and the protective effect of TDF and TDF/FTC did not differ between women and men. Adherence to the daily regimen, measured by dispensed doses taken and pill bottles returned, exceeded 96% for all three treatment groups. Rates of serious adverse events were comparable across the three study arms.

In Botswana, the TDF2 PrEP trial randomized 1,200 HIV-negative sexually active adults (45% women) to daily TDF/FTC or to placebo.[2] Twenty-four people taking placebo versus nine taking TDF/FTC became infected with HIV during the study to yield an overall protective efficacy of 63% for PrEP ($P = 0.0133$). An analysis limited to participants who became HIV-positive within 30 days of last medication determined that PrEP had a protective efficacy of 78% ($P = 0.0053$). Serious adverse event rates were similar with TDF/FTC and placebo (9.2% versus 8.5%, $P = 0.58$), though a significantly higher proportion of study participants taking TDF/FTC reported dizziness, nausea or vomiting. Adherence measured by pill count was similar in the two study arms, as were the proportions of participants with more than one sexual partner in the previous month.

Results of iPrEx, which randomized 2,499 HIV-negative MSM and transsexual women who have sex with men to TDF/FTC or placebo, were released before IAS 2011 and updated at the conference.[3,4] Study participants lived in North and South America, South Africa and Thailand. An intention-to-treat analysis considering all HIV infections throughout updated follow-up determined that study participants taking TDF/FTC PrEP had a 45% lower risk of infection than those taking placebo ($P = 0.0005$). A modified intention-to-treat analysis that included available data for all participants except those with HIV RNA detected in their enrollment sample determined that TDF/FTC reduced HIV acquisition risk 42% ($P = 0.002$).

Study participants who took TDF/FTC consistently enough to have measurable drug levels in blood had a 92% lower risk of HIV infection. Among the 366 participants (15%) who identified themselves as transgendered or who used female sex hormones, there were 11 HIV infections in the TDF/FTC group and 11 in the placebo group. Almost none of the transgendered participants had had sex-change surgery.

FEM-PrEP, a fourth PrEP trial not presented but often discussed at IAS 2011, found that daily TDF/FTC did not protect highly sexually active African women from HIV infection.[5] The

Implications section below discusses why FEM-PrEP results may have differed from the other three PrEP trials.

Women, Girls and HIV Investigator Prize and TB/HIV Research Prize

Milly Kaggwa Nanyombi (Uganda) is the winner of the Women, Girls and HIV Investigator Prize for her abstract, *Preventing HIV Infection among adolescents by addressing Cross Generational Sex (CGS) in Secondary Schools in Uganda*.

The US$2,000 prize is awarded to an investigator from a low- or middle-income country whose abstract demonstrates excellence in research and/or practice that addresses women, girls and gender issues related to HIV. The award is offered jointly by the IAS-Industry Liaison Forum and UNAIDS, and supported by the International Center for Research on Women and the International Community of Women Living with HIV/AIDS.

Sabine Margot Hermans (The Netherlands) is the winner of the IAS TB/HIV Research Prize for her abstract *Integration of HIV and TB services* results in earlier and more prioritized ART. Sponsored by the IAS, the aim of the US$2,000 prize is to generate interest and stimulate research on basic, clinical and operations research in TB/HIV prevention, care and treatment.

cART as Prevention

HPTN 052 involved 1,763 HIV-discordant couples with a CD4 count between 350 and 550 cells/mm^3 living in sub-Saharan Africa, Asia, or the Americas.[6,7] Investigators randomized the HIV-positive partners – half of them women – to begin combination antiretroviral therapy (cART) immediately or to delay treatment until the CD4 count fell to 250 cells/mm^3 or an AIDS-defining condition developed. When the trial DSMB recommended stopping HPTN 052, there were 28 HIV transmissions with a demonstrable genetic link between trial partners. One of these transmissions occurred in the immediate-cART arm and 27 in the delayed arm ($P < 0.001$). Those rates translated into a 96% lower risk of HIV transmission in the immediate-cART group, and that risk did not differ by gender.

Many will consider HPTN 052 a landmark study not only because it demonstrates that cART prevents HIV transmission, but because it is the first randomized trial to show that starting cART at a CD4 count above 350 cells/mm^3 reduces the risk of serious complications. Through a median follow-up of 1.7 years, 40 participants in the immediate-cART group and 65 in the delayed cART group had a study-defined clinical event. These results meant immediate cART reduced the risk of a clinical event by 40% ($P = 0.01$). Extrapulmonary TB accounted for most of this difference, with an incidence of 0.2 per 100 person-years in the immediate arm and 1.0 per 100 person-years in the delayed arm. Each study group had a 14% incidence of severe or life-threatening adverse events.

Results of a large cohort study bolstered the rationale for starting cART at a higher CD4 count.[8] This analysis focused on 66,147 HIV-positive COHERE Cohort members with CD4 counts measured just before or during cART-induced full suppression of HIV (HIV RNA <50 copies/mL). A statistical model that adjusted for relevant variables determined that the risk of AIDS or death for every 100-cell CD4 gain during cART was 65% lower for people with a starting CD4 count under 200 cells/mm^3, 19% lower for people with a starting count between 200 and 349 cells/mm^3, 26% lower for those with a starting count between 350 and 499 cells/mm^3 and 4% lower for those with a starting count above 500 cells/mm^3, and all of those associations were statistically significant.

Other HIV Prevention Strategies

Daily antiretrovirals are only the latest HIV prevention strategy assessed in randomized trials. In an IAS 2011 special session address, Anthony Fauci listed 10 prevention strategies (**Figure 2**),[9] most of which were subjects of new research presented at the conference. Results in several of these areas were particularly compelling.

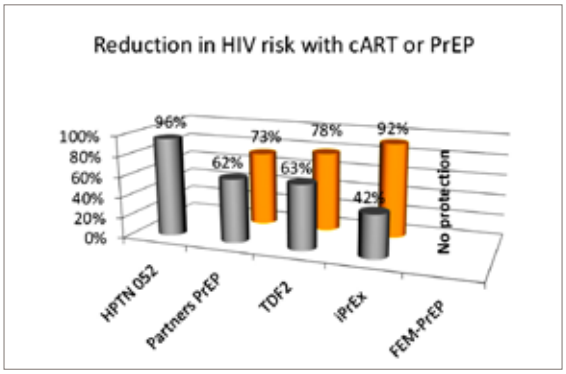

Figure 2. *Daily antiretrovirals emerged as a viable HIV prevention strategy at IAS 2011, but the conference also featured important new work on several other approaches, including microbicides, circumcision, PMTCT and an HIV vaccine. (Slide courtesy of Anthony S. Fauci, presentation MOSS0102.)*

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Microbicides

At the XVIII International AIDS Conference (AIDS 2010), CAPRISA 004 researchers unveiled data demonstrating that 1% tenofovir vaginal gel lowers the risk of HIV acquisition in sexually active African women by 39% compared with an inert gel.[10] Further analysis showed that women using tenofovir gel in CAPRISA 004 had a 51% lower risk of acquiring herpes simplex virus type 2 (HSV-2) infection.[11] A cell study demonstrated why tenofovir has this unanticipated and strong anti-HSV-2 activity.[12] Tenofovir 1% gel, the dose used in CAPRISA 004, lowered HSV-1 and HSV-2 infection titers by several orders of magnitude in human ex vivo lymphoid and cervical tissues infected only with HSV and in tissues coinfected with HSV and HIV-1. In addition, tenofovir diphosphate, the active metabolite of tenofovir, was generated in human cell cultures and inhibited HSV DNA polymerase.

Tenofovir concentrations achieved by topical vaginal application are much higher than systemic levels generated by the oral drug (TDF), which was used in the three PrEP trials. Inhibition of HSV-1 and HSV-2 protects women from these sexually transmitted viruses and could contribute to protection from HIV.[11]

Circumcision

Several years ago a trial in South Africa became the first of three randomized trials to show that circumcision of sexually active heterosexual men significantly lowers their risk of HIV acquisition.[13] At IAS 2011, researchers who conducted that trial presented the first evidence that rollout of medical male circumcision programmes in Africa can decrease the spread of HIV in endemic communities.[14]

The new analysis involved 1,198 South African men, aged 15 to 49, randomly sampled, interviewed and tested for HIV in 2007, before the circumcision programme began, and 1,178 men of the same age studied in late 2010, three years into the circumcision programme. Among men 15 to 49 years old, adjusted HIV prevalence was 55% lower in the 2010 group than in the 2007 group (adjusted prevalence ratio 0.45, 95% confidence interval [CI] 0.30 to 0.63). Among men 15 to 34 years old, adjusted HIV incidence was 76% lower in the 2010 group (adjusted incidence ratio 0.24, 95% CI 0.00 to 0.66). The investigators calculated that without the intervention (if no men were circumcised), HIV prevalence among 15- to 49-year-old men would have been 25.1% higher than with the intervention (95% CI 13.1% to 39.1%), and HIV incidence among 15- to 34-year-old men would have been 57.9% higher (95% CI 17.0% to 131%). Sexual behavior (such as consistent condom use) did not change in these men after they were circumcised.

Vertical HIV Transmission

PMTCT with one or more antiretrovirals has reduced the risk of perinatal HIV transmission to the low single digits in high-income, low HIV prevalence countries. At IAS 2011, an African study showed for the first time that PMTCT can have the same impact in a country with high HIV prevalence.[15] This 2010 national cross-sectional, facility-based survey involved 9,915 infant-caregiver pairs in South Africa, which launched its PMTCT in 2002. Dried blood spot analysis identified 3,003 HIV-exposed 4 to 8 week-old infants (30.3%), 2,958 of them with HIV DNA results. The investigators calculated that the national HIV vertical transmission rate in infants this age was 3.5% (95% CI 2.9% to 4.1%).

Mixed breastfeeding versus exclusive breastfeeding raised the risk of HIV transmission 60% (adjusted odds ratio [AOR] 1.6, 95% CI 1.0 to 2.5). Three approaches to antiretroviral prophylaxis magnified the risk of HIV transmission when compared with maternal cART: (1) either maternal antiretroviral prophylaxis or infant antiretroviral prophylaxis (AOR 5.2, 95% CI 2.7 to 10.0); (2) 10 or fewer weeks of maternal antiretroviral prophylaxis and infant antiretroviral prophylaxis (AOR 2.4, 95% CI 1.2 to 5.1); or (3) 11 to 30 weeks of maternal antiretroviral prophylaxis and infant antiretroviral prophylaxis (AOR 1.7, 95% CI 0.9 to 3.5). (For more data on cART during pregnancy and postpartum, see *cART for Pregnant Women/Mothers* below.)

Pooled analysis of five randomized trials determined that infant prophylaxis with nevirapine alone or nevirapine plus zidovudine lowers the risk of HIV acquisition by 71%.[16] The study involved 5,396 mother-infant pairs in which infants of HIV-positive mothers were HIV-negative at birth and began prophylaxis with one of four regimens: nevirapine for six weeks, 14 weeks or 28 weeks, or nevirapine plus zidovudine for 14 weeks. At week 28, compared with control infants, infants receiving six weeks of nevirapine had a 20% lower risk of HIV infection (hazard ratio [HR] 0.80, 95% CI 0.53 to 1.21, not significant), infants receiving 14 weeks of nevirapine had a 64% lower risk (HR 0.36, 95% CI 0.23 to 0.57, $P < 0.001$), infants receiving 14 weeks of nevirapine/zidovudine had a 51% lower risk (HR 0.49, 95% CI 0.32 to 0.75, $P = 0.001$), and infants receiving 28 weeks of nevirapine had a 71% lower risk (HR 0.29, 95% CI 0.15 to 0.54, $P < 0.001$). Maternal CD4 count below 350 cells/mm^3 doubled the risk of HIV transmission (HR 2.14, 95% CI 1.67 to 2.73, $P < 0.001$), and every 1-kg higher infant birth weight lowered the transmission risk 36% (HR 0.64, 95% CI 0.48 to 0.85, $P = 0.002$).

Impact of contraception

A seven-country prospective study in Africa identified one factor critical to the risk of HIV acquisition or transmission: hormonal contraception.[17] Among 3,790 HIV-discordant heterosexual couples, the woman was HIV-negative in 1,314 couples. HIV acquisition rates were 6.61 versus 3.78 per 100 person-years in women currently using versus not using hormonal contraception. In an analysis adjusted for age, viral load, sex without a condom and pregnancy, women using contraception had double the risk of acquiring HIV (HR 1.98, 95% CI 1.06 to 3.68, $P = 0.03$). Among 2,476 couples in which the man was the HIV-negative partner, rates of HIV transmission from women to men were 2.61 versus 1.51 per 100 person-years when the woman was currently using versus not using hormonal contraception. Male partners of women using hormonal contraception had double the risk of acquiring HIV (HR 1.97, 95% CI 1.12 to 3.48, $P = 0.02$), apparently because these women were more likely to have detectable genital viral loads and higher genital viral loads.

Both injectable and oral hormonal contraceptives raised the risk of HIV acquisition or transmission, though only injectable contraceptives raised the risk significantly in subgroup analyses. Genital HIV RNA levels were significantly higher in HIV-positive women using hormonal contraception than in those not using contraception. These findings could help explain why TDF/FTC did not protect women from HIV in the FEM-PrEP trial but did in Partners PrEP and TDF2, as discussed in the Implications section below.

HIV vaccines

Two speakers at IAS 2011 summarized potentially promising developments in HIV vaccinology.

In a plenary address,[18] US National Institutes of Health Vaccine Director Gary Nabel noted that a placebo-controlled phase 3 trial in Thailand offered the first evidence that a vaccine can prevent HIV in humans, although the tested canarypox vector/gp120 subunit vaccine lowered infection risk only 31% and had limited protective duration.[19] Nabel highlighted development of resurfaced stabilized core proteins that can be used as probes for human neutralizing antibodies and templates for immunogens. VRC01, a panreactive antibody identified in this way, neutralizes 90% of natural circulating viruses[20] and confers sterile protection against mucosal challenge in nonhuman primates. Nabel explained that VRC01 works so well because it partially mimics CD4, binding to the HIV-1 gp120 envelope protein at an invariant site of initial CD4 attachment.

Susan Zolla-Pazner, at New York University, is also searching for broadly neutralizing antibodies that target the V2 and V3 loops of the HIV-1 envelope.[21] Like Nabel and colleagues, she is focusing on sequences in these regions that vary little from strain to strain of HIV-1 and so could be targets for broadly neutralizing antibodies. In test tube studies Zolla-Pazner and coworkers demonstrated that antibodies they identified protect against 50% of a panel of HIV-1 strains, and these antibodies remain detectable 60 weeks after the last boost. The vaccine they used is a

IAS and ANRS Young Investigator Award winners, Anandi Sheth, Lilanganee Telisinghe, Musa Ngayo and Xu Yu

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Women's Prevention Revolution Demonstration

gp120 DNA-based prime followed by a boost with Env V3 attached to a cholera toxin B protein scaffold immunogen.

Implications of Prevention Research

Along with favorable results from the CAPRISA 004 microbicide trial, 5 of the four antiretroviral prevention trials presented at IAS 2011 offer solid evidence that oral or topical antiretrovirals significantly and substantially reduce the risk of HIV acquisition or transmission. Implications of these seminal studies for research, policy and practice are as weighty and manifold as the results themselves.

Writing about these studies in a *Lancet* issue published in tandem with IAS 2011, former IAS President Julio Montaner noted that the findings make it clear "that treatment as prevention has progressed from a testable hypothesis to an urgent implementation priority".[22] Whether PrEP or cART should or can be implemented is the fraught question faced by policymakers and clinicians everywhere.

In 2010 UNAIDS estimated that fewer than one third of those who need cART according to World Health Organization (WHO) criteria get treated.[1] If all people with HIV were to begin cART regardless of CD4 count — a prevention measure made reasonable by HPTN 052 — where will the world find the additional money, health workers and infrastructure needed to treat them? If millions of at-risk heterosexuals and MSM decide they want to try one- or two-drug PrEP, the question becomes even harder to answer. Task shifting (assigning the care of certain patients to nonphysician health workers) could alleviate the physician shortage, though work presented at IAS 2011 suggests this strategy requires further study.[24] As a group of prevention experts observed in a review dissecting "the new prevention research agenda,"[25] a tenacious global economic slowdown makes future HIV/AIDS funding commitments unclear.

The four antiretroviral prevention trials raise several immediate questions that researchers must address:

1. Are two drugs needed for effective PrEP or, as Partners PrEP found, will one do just as well?
2. Why did PrEP work in heterosexual women and men and in MSM, but not in highly sexually active women in FEM-PrEP[2] or in transgender women in iPrEx?
3. Do the sexually active African women in FEM-PrEP[2] and the transgender women in iPrEx have something in common, such as worse adherence than Partners PrEP and TDF2 participants? Or did FEM-PrEP women and iPrEx transgenders have altered hormone levels

affecting drug transport in the mucosa resulting from hormonal contraceptives or from self-administered hormones? (While 66% of FEM-PrEP participants were using injectable hormonal contraceptives, 30% were using oral contraceptives. In contrast, 10% of Partners PrEP participants were using oral contraceptives, 26% injectables and 8% implants.)
4. What is the relative efficacy of a vaginal gel and an oral medication for preventing HIV in women?
5. Will PrEP work in people who inject drugs?
6. Should WHO guidelines on when to start cART be revised to reflect the lower transmission and slower progression in HPTN 052 participants who started treatment with a CD4 count between 350 and 550 cells/mm^3?

The ongoing randomized VOICE trial addresses questions one and four (clinicaltrials.gov NCT00705679), and continued follow-up in Partners PrEP could help answer question one. Research already shows that 1% tenofovir vaginal gel achieves tissue concentrations 1000 times higher than achieved with oral tenofovir.[26] Another ongoing randomized trial addresses question five (clinicaltrials.gov NCT00119106). Nancy Padian and colleagues observed in the special edition of the *Lancet*, issued in conjunction with IAS 2011, that research must also explore "implementation challenges that preclude scale-up of prevention strategies known to be effective — specifically HIV testing, voluntary medical male circumcision and prevention of mother-to-child transmission"[25].

Clinicians in regions with the resources to implement PrEP with TDF or TDF/FTC already face the challenge of what to advise at-risk patients who want to try PrEP. In the United States, the Centers for Disease Control and Prevention (CDC) issued preliminary advice on when and how PrEP might be used in practice.[27] Providers must also remember that all well-run HIV prevention trials provide the intervention being studied as part of a comprehensive prevention package. Thus health workers must stress that PrEP or a microbicide or circumcision *alone* should not be relied on exclusively to prevent HIV. Because TDF is a critical component of first- and second-line cART across the world, PrEP that relies on other antiretrovirals, such as HIV entry inhibitors, may make more sense.

Demonstration that medical male circumcision can decrease HIV prevalence by 25% and HIV incidence by 58% in sexually active heterosexual men in HIV-endemic regions should bolster government resolve to make circumcision part of overall HIV prevention efforts in these regions. Other research presented at IAS 2011 showed that circumcision campaigns in HIV-endemic regions meet with high acceptance rates among young men and can exceed targets by thousands of men.[28] Modeling indicated that the six-week campaign in Tanzania prevented 2,300 HIV infections.

The finding that South Africa's PMTCT programme reduced vertical HIV transmission to below 4% in the first two months after birth confirms that this prevention strategy works as well in sub-Saharan Africa as in high-income countries. Yet PMTCT coverage remains below 50% in many countries with high HIV prevalence, despite significant resources and focus over the past decade.[29]

Trial-confirmed success of several HIV prevention strategies raises questions about how scant resources should be applied to continuing HIV vaccine research. Although progress in this field can seem agonizingly slow, HIV vaccine expert Gary Nabel argued that vaccine research should continue for two reasons: once an effective vaccine is given, protection lasts a lifetime; and an effective HIV vaccine would be among the most cost-effective medical interventions.

Researchers argued that the finding that hormonal contraception heightens the risk of HIV transmission and acquisition should not weigh against judicious use of contraception because "the benefits of effective hormonal contraceptive methods are unequivocal;" rather, they advised that "women should be counseled about potential increased risk of HIV-1 acquisition and transmission with hormonal contraception, particularly injectable methods and about the importance of dual protection with condoms to decrease HIV-1 risk". Investigators called for greater use of long-acting contraceptive methods with lower doses of exogenous hormones or nonhormonal methods, such as intrauterine devices.

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TRACK D: OPERATIONS RESEARCH

Expanding Testing, Counselling and HIV Knowledge

Improving uptake of HIV testing and counselling (HTC) is key to engaging people in prevention, care and treatment services. Between November 2006 and August 2010, researchers tracked a prospective cohort of 4,877 adults (53% women) in Durban (in both urban and exurban areas), evaluating HIV testing behaviour and HIV knowledge using baseline and annual questionnaires.[1] Prevalence declined from 63.5% of enrollees at baseline to 39.2% in the final year of the study (linear trend $p<0.001$) while the proportion of study participants who reported prior HIV testing increased from 13.3% to 42.4% ($p<0.001$), including an increase in participants reporting multiple prior tests (from 4.1% to 17.2%). The study also revealed that HIV knowledge had improved (e.g., knowing that ART could treat HIV disease rose from 80.3% to 95%); however, important gaps remain as 25% of participants indicated they did not know how HIV could be prevented (including how vertical transmission could be prevented). These findings raise questions about the quality of behavioural and risk reduction counselling provided during HIV screening.

IAS/ANRS Young Investigator Award Winners:

Track A: Basic Sciences: Xu Yu, China, *Unique mechanisms of CD4 T cell homeostasis in HIV-1 elite controllers*

Track B: Clinical Sciences: Musa Ngayo, Kenya, *Association of abnormal vaginal flora with male-to-female HIV-1 transmission among HIV-1 discordant couples in sub-Saharan Africa*

Track C: Prevention Science: Anandi Sheth, USA, *Genital secretions of HIV-1 infected women on effective antiretroviral therapy contain high drug concentrations and low amounts of cell-free virus*

Track D: Operations and Implementation Research: Lilanganee Telisinghe, UK, *Antiretroviral therapy roll-out in an African prison: It can be done*

The awards are jointly funded by the IAS and the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) and provide US$2,000 to young researchers who demonstrate innovation, originality and quality in the field of HIV and AIDS research. To be eligible, the presenting abstract author must be under 35 years of age.

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Stefano Vella and Myron Cohen, IAS 2011 Official Press Conference, *Treatment is Prevention, The Proof is Here*

A home-based HTC programme in Suba District, Uganda used a family-based approach to offering HTC.[2] The programme (which delivered HBTC from 2007 to 2009) in a poor, rural district, arranged home-based visits in advance, testing 68,315 individuals (including 10,790 couples): 42.9% were male, 57.1% were female and 30.5% were under 18 years of age. Eight-four per cent of households accepted the HTC offer (which included a counselling session for family members), and 60.3% of individual members of those households were first-time testers. HIV prevalence in this cohort was 10.5% (12.3% female; 8.2% male), lower than the national estimated prevalence of 30%. Individuals testing HIV-positive were referred for clinical assessment and support (to either ART or PMTCT programmes) and those testing HIV-negative were referred to risk reduction support groups. The majority of those testing HIV-positive (66.1%) were unaware of their HIV status. The success of this programme in Suba (and results from a similar programme in Bushenyi District) resulted in a decision to scale up home-based HTC in six other Ugandan districts.[3] The initial pilots have now become a platform of multi-component, combination HIV prevention and care efforts, which have been successful in significantly expanding the reach of HCT and referral to care.

Closing Gaps in the Cascade of Retention

Enrolling patients early in treatment programmes – at CD4+ cell counts above 200 mml^3 – significantly reduces morbidity and mortality.[4,5] A number of studies focused on the ongoing challenge of improving uptake and retention in

Treatment is Prevention, the Proof is Here

care, using HIV HTC as the gateway to care. Interventions included expanding HTC delivery (and modes of delivery) in a range of settings and referral for clinical assessment, staging and, if clinically eligible, placement and retention in ART programmes. Over time, there have been gradual improvements in ART programme retention; Mathew Fox summarized meta-analyses published in 2007 and (in process) 2010, indicating that retention (defined as in care 24 months after enrolment) had risen from a median of 60% to 70% over those three years.[6] However, those aggregate numbers account only for those lost to follow-up (LTFU) who were enrolled in ART programmes, masking wide variances among country ART and PMTCT programmes, and not accounting for significant attrition at each stage of the pre-ART cascade. A South African study evaluated whether using a rapid POC CD4+ technology in a mobile HTC unit would improve referral to care for those testing HIV-positive (using eight weeks as the measure between testing and first visit at referral)[7]: one arm of the study received standard HTC (n=197) and the other received HTC and CD4+ cell counts (311). The proportion of both groups reached by phone with their test results was 63%, but a substantially larger proportion of those who also received their CD4+ count information completed their referral visit to a clinic: a 68% increase in referral completion from 38.5% to 64.7% compared to those who received HCT alone.

A Malawi study aimed at evaluating whether early infant testing and diagnosis (EID) is feasible in a rural setting confirmed the extent of attrition within two primary care clinics providing PMTCT in Bantyre, Malawi.[8] The 1,257 pregnant women who were diagnosed HIV-positive (out of a total of 7,570 participating in the PMTCT programme) were informed about the importance and availability of EID during antenatal care. Of all HIV-exposed infants, 891 (70.9%) presented for EID, and dried blood spot (DBS) analysis indicated 14.4% (128) were HIV-positive. Despite active outreach by the clinic, only 89% of these (114) received the test results. DBS re-testing and viral load quantification among 101 infants confirmed HIV infection in 82 (an HIV incidence of 11.6%). Of 67 infected infants with available follow-up information, 48 (71.6%) initiated ART (at either one of the primary care clinics or an outpatient clinic) at a median age of 4.7 months, resulting in only 37.5% of confirmed HIV-infected infants being placed on ART.

The Tingathe Programme in Malawi used trained community health workers (CHWs) to address the enormous challenge of improving early paediatric diagnosis and treatment in a country with 100,000 infants and children living with HIV (most of them undiagnosed), PMTCT programme coverage of only 35% (with over 50% loss to follow-up) and 30,000 new infant infections each year.[9] In the 2.5 years since the inception of Tingathe, 15,997 children were tested and 4,766 were diagnosed HIV-positive. Enrolment of children on ART increased from less than 50 to 2,425, with less than 5% lost to follow-up. This programme has since expanded to incorporate all PMTCT programme components, with a CHW assigned to an HIV-positive pregnant woman immediately after pregnancy is confirmed to help ensure the prospective mother and (following delivery) infant access relevant components of PMTCT care and treatment. Results after the first year of implementation indicated that 99% (740) of women enrolled in the PMTCT programme received ARV prophylaxis to prevent vertical transmission, 98% (734) of infants received ARV prophylaxis following delivery and 77% (568) were enrolled in care and treatment. The proportion of infants and children on ART rose from 0.7% to 8.8% ($p<0.0001$), demonstrating that innovation and modest investments can expand health workforce capacity and have dramatic results in reducing vertical transmission and improving paediatric care and treatment by supporting patients throughout the continuum of care.

Françoise Barré-Sinoussi, *Towards an HIV Cure* Press Conference

A South African study provided helpful insights into how children and adolescents can be retained in care and remain adherent to their ARV drug regimen at the primary health care level.[10] Beginning in 2004, community-based adherence and support counsellors called Patient Advocates (PAs) were trained to address a number of clinical and psychosocial support issues for patients (including pre-ART education and support), linking them to relevant health services as well as providing adherence counselling following ART initiation. The study enrolled 3,643 ART-naïve children and adolescents at 47 sites in four South African provinces (January 2004 to September 2009), with 323 (9.1%) linked to PAs and 3,240 (90.9%) without PAs. While there were no statistically significant differences in virologic suppression or CD4+ cell count between the two arms at the end of the study, patients with PAs were approximately 50% more likely to be retained in care (Adjusted hazard of attrition of patients with PAs: 0.57 (CI: 0.35–0.94) and 65% less likely to die (Adjusted hazard of mortality of patients with PAs: 0.40 (CI: 0.15–1.06).

Delivering Better Diagnostics

HIV and TB diagnostic technologies (for both diagnosis and clinical monitoring) have often been the Achilles heel of HTC and treatment. Substantial turnaround times for test results and variability in the reliability and sensitivity of technologies contribute to loss to follow-up and mortality at several points in the retention-in-care cascade. A Track D Late Breaker session included lessons learned from South Africa's rollout of 30 GeneExpert MTB/RIF diagnostic platforms to microscopy facilities, beginning with 25 sites in nine regions with the highest burden of TB.[11] South Africa has 20% of the world's TB cases, with 70 to 80% of suspect TB cases co-infected with HIV. Of the 50,093 individuals tested for TB from March to June 2011, 8,591 tested TB-positive and 630 were resistant to rifampicin, the standard first-line TB drug. The results of the Phase I rollout significantly increased early screening for TB and for potential MDR cases, providing an opportunity for earlier clinical intervention with appropriate first or second-line treatment as well as ART initiation in co-infected patients. As a result, changes are underway to the National TB Programme, with plans to facilitate HIV/TB integration at the laboratory, clinic and programmatic level with a rapid, large-throughput, real-time technology that delivers reliable and sensitive outputs. A cost-effectiveness analysis of the

rollout indicated that, despite the significant initial capital investment, it was highly cost-effective, accounting for 0.3% of total programme costs and had an incremental cost effectiveness ratio of $1,860/year-of-life saved (YLS).[12]

Decentralization and Integration

A number of studies evaluated the impact of decentralizing various HIV services, with mixed results. A study reported on the experience of six African countries that have decentralized laboratory services to 229 sites in mostly rural (66%) or peri-urban (9%) settings over the past seven years to provide Point-of-Care (POC) laboratory capacity to primary care centres and health posts as well as larger tertiary care centres.[13] Laboratory capacity included rapid HIV diagnosis, immunological staging (absolute CD4+ counts and percentages) and diagnosis of major opportunistic infections (OIs) such as TB and malaria. The decentralization of care and treatment services over this time period resulted in a rapid scale-up of those on ART from less than 25,000 in Year 1 to 355,561 at the end of Year 7 (with 201,697 in care, but not on ART). Loss to follow-up was less than 5%; average viral suppression was 88.7% across all sites in the six countries, with a low general mortality of 8.4%.

Normative Guidance: HIV Testing and Counselling Among Serodiscordant Couples

WHO couples testing and counselling guidelines, originally due for release in conjunction with IAS 2011, are now in the process of being reviewed and revised in light of results from the HPTN 052, iPrex and TDF2 studies. The efficacy of cART in reducing HIV transmission among serodiscordant heterosexual couples has raised complex operational, financial and ethical issues for normative guidance, including how a 'couple' is defined for the purposes of the guidelines. Some countries, such as Rwanda, are already in the process of changing treatment protocols to recommend treating the HIV-positive partner with cART, irrespective of treatment eligibility based on current WHO guidelines, raising ethical issues about whether this is, in effect, helping a specific population 'jump the queue' and adding to health inequity. At a Satellite Session hosted by WHO on the issue, Bernard Hirnschall, Director of the HIV Department, confirmed that WHO will release guidelines in 2011 that incorporate the results of HPTN 052 in its couples counselling recommendations.

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Workshop, *Towards an HIV Cure*, Insight into Residual Viral Replication, Establishment of Reservoirs and Understanding Mechanisms of Persistence

A retrospective cohort study evaluated the characteristics of clinics with attrition rates in two Mozambique provinces (January 2006 to June 2008).[14] Beginning in 2004, Mozambique began to decentralize HIV care and treatment from vertical (specialty) HIV clinics to integrated clinics (offering primary health care services in addition to HIV care). A total of 11,793 patients from 18 clinics were studied. The overall attrition rate was 39.22 per 100 person-years. After adjusting for patient characteristics and pharmacy staff levels, patients attending vertical clinics had a lower risk of attrition (HR=0.84, 95% CI: 0.73-0.97; p=0.015). The five-year Researching Equity and Access to Health care (REACH) project in South Africa also evaluated the impact of 'down-referral' of HIV services from hospitals (following initial ART initiation and six months of follow-up at the hospital clinic);[15] 220 patients continued to access care and treatment at the hospital, while 109 were 'down-referred' to local clinics. The results indicated that down-referral saves travel time for the patients and reduced costs to the health care system, but that patients who were 'down-referred' sought out additional health care providers, such as traditional healers, and had significantly greater out of pocket expenses than those attending the hospital-based clinic.

In an evaluation of clinical management at a large urban HIV clinic in Uganda which integrated its TB and HIV services, HIV and TB co-infected patients were initiated on ART earlier than before integration (median 44 days versus 101 days before integration; p=0.01).[16] Both survival and retention in care improved significantly, with only 25% dying or lost to follow up before ART initiation compared to 75% before integration.

Implications of Operations Research

Data from studies reporting on a diverse range of approaches aimed at increasing HTC uptake and reducing loss to follow-up provide strong evidence that home-based HTC, mobile HTC units and expanding the role of community-based services throughout the continuum of care are key to bringing HIV prevention, care and treatment programmes to scale. While the current economic climate continues to place resource constraints on HIV programmes, IAS 2011 provided new insights into how to deliver efficient and effective services with uptake and retention, even in rural or remote settings.

As some of the studies outlined above underscore, more research is required to understand how best to decentralize services to maximize efficiencies, expand access to HIV services and maintain high-quality care and support. The Malawi study on EID and treatment underscored the multiple points in the retention-in-care cascade that HIV programme managers, health care providers and community health workers must address to reduce the significant proportion of individuals lost to follow up in both pre-ART care and following ART initiation.

A number of studies address various aspects of the WHO/UNAIDS Treatment 2.0 initiative, which aims to optimize drug regimens, improve access to rapid, reliable POC and laboratory diagnostics, decentralize and better integrate service delivery with other components of the health care system, reduce costs and mobilize communities.[17] A number of studies and programme evaluations presented at IAS 2011 provided evidence that, even in resource-limited settings, significant improvements in HCT uptake and retention in both pre-ART care and care following ART initiation are feasible goals.

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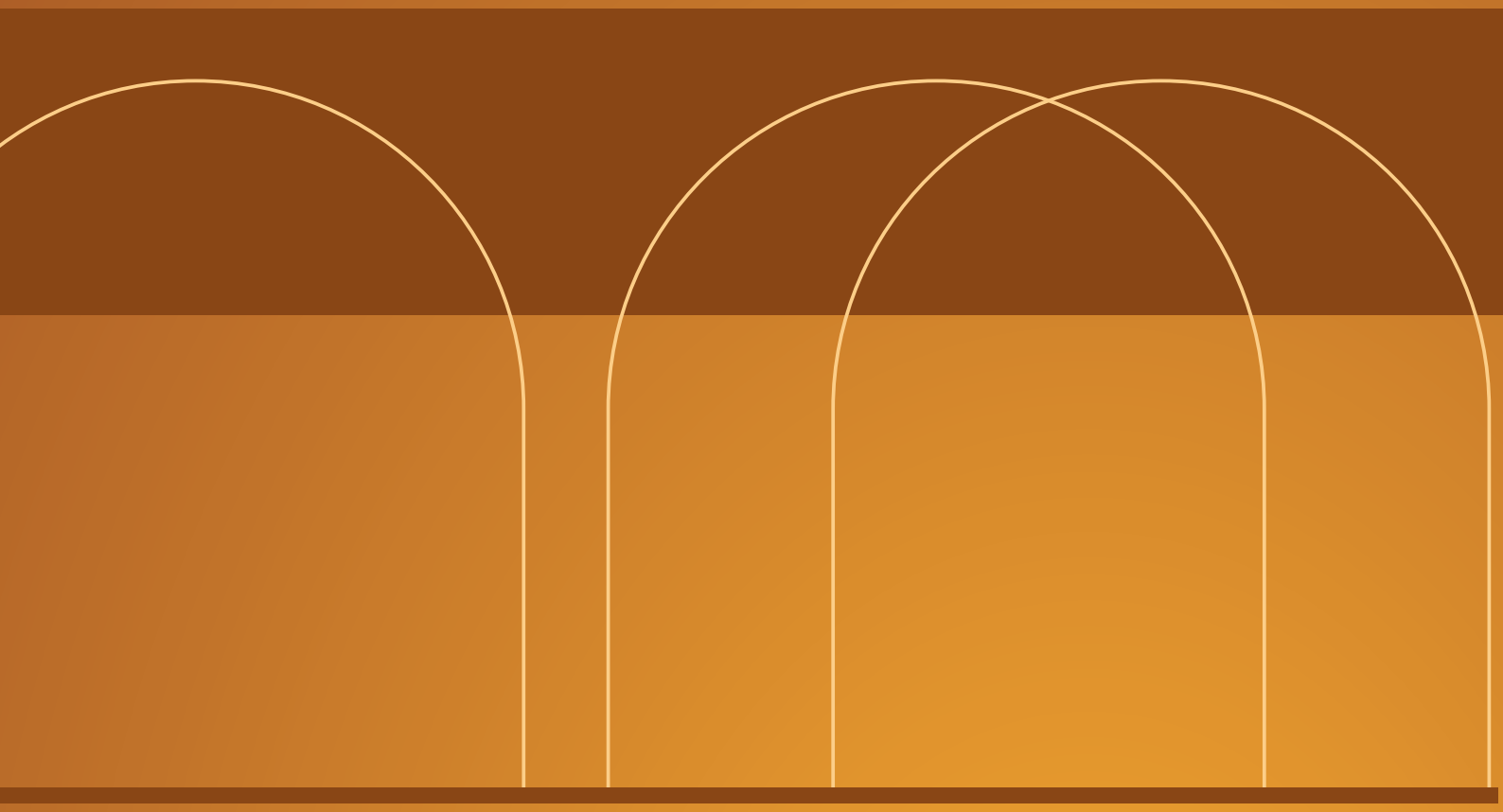

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