

## *HIV This Week*: what scientific journals said

Welcome to the 62nd issue of *HIV This Week*! In this issue, we cover **behaviour change** (multiple sources of evidence reveal what actually did happen in Uganda), **prevention** (four windows of opportunity for HIV prevention; insights from mathematical modelling on treatment as prevention), **microeconomics** (out-of-pocket costs gulf the effects of free antiretroviral drugs in China; hungry kids in affected households in Cambodia), **tuberculosis** (progress in diagnostics; BCG vaccine-induced complications in kids starting antiretroviral treatment), **intimate partner violence** (childhood exposures to violence among South African men associated with perpetration of violence; news from the morgue in the Republic of Congo reveals murder of HIV-positive women); **treatment** (drug resistance after first-line highly active antiretroviral therapy; what factors increase regimen durability), **HIV testing** (rapid testing makes no inroads in a rural South African community), **injecting drug use** (increases in the number of people who inject drugs and HIV prevalence among them), **epidemiology** (mature epidemics in 5 African countries: what role does commercial sex play?), **faith-based organisations** (time for real change in Malawi), **pathogenesis** (news from the SMART trial on inflammation and mortality; why we need to know more about HIV immunopathogenesis), **microbicides** (intravaginal rings find favour in Kenya, what we know and don't know about mucosal HIV transmission), **prevention trial conduct** (improving recruitment and retention in virtual world HIV prevention trials), and **youth** (urban adolescent school girls have much to learn in India).

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### **1. Behaviour Change**

Kirby D. Changes in sexual behaviour leading to the decline in the prevalence of HIV in Uganda: confirmation from multiple sources of evidence. *Sex Transm Infect.* 2008;84 Suppl 2:ii35-41.

Kirby set out to identify the changes in sexual behaviour that led to the dramatic reduction in the prevalence of HIV in Uganda in the early 1990s. Seven different types of evidence were examined: (1) models of HIV prevalence and incidence in Kampala and other sentinel sites in Uganda; (2) reports of behaviour change in the primary newspaper in Uganda; (3) surveys with questions about perceptions of personal behaviour change; (4) large demographic and health surveys (DHS) collected in 1988/9 and 1995 and large Global Program on AIDS (GPA) surveys in 1989 and 1995 with questions about reported sexual behaviour; (5) smaller less representative surveys of reported sexual behaviour collected in other years; (6) reports of numbers of condoms shipped to Uganda; and (7) historical documents describing the implementation of HIV prevention programmes in Uganda. All seven types of data produced consistent evidence that people in Uganda first reduced their number of sexual partners prior to or outside of long-term marital or cohabiting relationships, and then increased their use of condoms with non-marital and non-cohabiting partners. Consistent with basic theories about transmission of sexually transmitted infections, first reducing the number of sexual partners and breaking up sexual networks and then reducing the chances of HIV transmission with remaining casual partners by using condoms can be achieved and can dramatically reduce the sexual transmission of HIV in generalised epidemics. **Editors' note: HIV incidence in Uganda began declining from a peak in 1987-88 and then declined more rapidly after 1992-93. Although each of the seven types of evidence presented here has limitations, together they paint a convincing picture that people restricted their sexual activity outside long-term marital and cohabiting relationships and then increased condom use with casual sexual partners when condom availability improved with the arrival in the early 1990s of large shipments of condoms. The debates about 'the one thing' that led to Uganda's historical fall in HIV prevalence are put to rest by this article highlighting the importance of combination prevention, including a good dose of political leadership, in stimulating and sustaining incidence declines.**

## **2. Prevention**

Cohen MS, Kaleebu P, Coates T. Prevention of the sexual transmission of HIV-1: preparing for success. *J Int AIDS Soc.* 2008;11(1):4.

There are four opportunities for HIV prevention: before exposure, at the moment of exposure, immediately after exposure, and as secondary prevention focused on infected subjects. Until recently, most resources have been directed toward behavioural strategies aimed at preventing exposure entirely. Recognizing that these strategies are not enough to contain the epidemic, investigators are turning their attention to post-exposure prevention opportunities. There is increasing focus on the use of antiretroviral treatment-either systemic or topical (microbicides)-to prevent infection at the moment of exposure. Likewise, there is growing evidence that antiretroviral treatment of infected people could serve as prevention as well. A number of ongoing clinical trials will shed some light on the potential of these approaches. Above all, prevention of HIV requires decision-makers to focus resources on strategies that are most effective. Finally, treatment of HIV and prevention of HIV must be considered and deployed together. **Editors' note: This excellent review of the prevention of sexual HIV transmission focuses on a menu of options driven by scientific results rather than ideology. Condoms and male circumcision have not reached their full prevention potential and the ecological evidence on the population-level benefits of**

antiretroviral treatment is mixed. Further, the very short time between HIV exposure, infection, and viral replication with seeding of reservoirs poses a major challenge for vaccine development. Pre-exposure prophylaxis gets antiretroviral protection on board before exposure to prevent infection at the time of exposure - it works for mother-to-child transmission so there are high hopes that it will enter the scientifically-validated combination prevention armamentarium for sexual transmission in coming years. Watch this space.

Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2008 Nov 26. [Epub ahead of print].

Roughly 3 million people worldwide were receiving antiretroviral therapy at the end of 2007, but an estimated 6.7 million were still in need of treatment and a further 2.7 million became infected with HIV in 2007. Prevention efforts might reduce HIV incidence but are unlikely to eliminate this disease. Granich and colleagues investigated a theoretical strategy of universal voluntary HIV testing and immediate treatment with ART, and examined the conditions under which the HIV epidemic could be driven towards elimination. They used mathematical models to explore the effect on the case reproduction number (stochastic model) and long-term dynamics of the HIV epidemic (deterministic transmission model) of testing all people in their test-case community (aged 15 years and older) for HIV every year and starting people on antiretroviral treatment immediately after they are diagnosed HIV positive. They used data from South Africa as the test case for a generalised epidemic, and assumed that all HIV transmission was heterosexual. The studied strategy could greatly accelerate the transition from the present endemic phase, in which most adults living with HIV are not receiving antiretroviral treatment, to an elimination phase, in which most are on antiretroviral treatment, within 5 years. It could reduce HIV incidence and mortality to less than one case per 1000 people per year by 2016, or within 10 years of full implementation of the strategy, and reduce the prevalence of HIV to less than 1% within 50 years. The authors estimate that in 2032, the yearly cost of the present strategy and the theoretical strategy would both be US\$1.7 billion; however, after this time, the cost of the present strategy would continue to increase whereas that of the theoretical strategy would decrease. They conclude that universal voluntary HIV testing and immediate antiretroviral treatment, combined with present prevention approaches, could have a major effect on severe generalised HIV epidemics. This approach merits further mathematical modelling, research, and broad consultation. **Editors' note: This mathematical modelling of universal voluntary testing and antiretroviral treatment at HIV diagnosis regardless of CD4 count in a southern Africa-like epidemic setting is provoking lively debate. Two accompanying commentaries highlight the pros and cons of such a theoretical strategy. Information on the clinical benefits of early treatment for individuals is urgently needed as it unclear whether people would start medication for public health benefit alone. The idea of antiretroviral drugs for prevention is not new. Antiretroviral pre-exposure prophylaxis of mother-to-child transmission and post-exposure prophylaxis for accidental HIV exposure are standard practices while trials of both oral and topical antiretroviral pre-exposure prophylaxis are currently underway in diverse populations. The HPTN 052 trial assessing the effect of index partner treatment on sexual transmission will also provide needed data on the benefits of early versus delayed antiretroviral therapy. In the**

meantime, given that antiretroviral drugs already play a role in HIV prevention, they are part of combination prevention. Thoughtful messaging to ensure good comprehension of their relative contribution to combination HIV prevention can help minimise harmful behavioural risk compensation, provide a degree of reassurance to many on effective treatment, and reinforce the smart idea of combining methods for better prevention of sexual transmission.

### 3. *Micro-Economics*

Moon S, Van Leemput L, Durier N, Jambert E, Dahmane A, Jie Y, Wu G, Philips M, Hu Y, Saranchuk P. Out-of-pocket costs of AIDS care in China: are free antiretroviral drugs enough? *AIDS Care*. 2008;20(8):984-94.

Financial access to HIV care and treatment can be difficult for many people in China, where the government provides free antiretroviral drugs but does not cover the cost of other medically necessary components, such as lab tests and drugs for opportunistic infections. This article estimates out-of-pocket costs for treatment and care that a person living with HIV in China might face over the course of one year. Data comes from two treatment projects run by Médecins Sans Frontières in Nanning, Guangxi Province and Xiangfan, Hubei Province. Based on the national treatment guidelines, Moon and colleagues estimated costs for seven different patient profiles ranging from WHO Clinical Stages I through IV. They found that patients face significant financial barriers to even qualify for the free antiretroviral treatment program. For those who do, HIV care and treatment can be a catastrophic health expenditure, with cumulative patient contributions ranging from approximately US\$200-3939/year in Nanning and US\$13-1179/year in Xiangfan, depending on the patient's clinical stage of HIV infection. In Nanning, these expenses translate as up to 340% of an urban resident's annual income or 1200% for rural residents; in Xiangfan, expenses rise to 116% of annual income for city dwellers and 295% in rural areas. While providing antiretroviral drugs free of charge is an important step, the costs of other components of care constitute important financial barriers that may exclude patients from accessing appropriate care. Such barriers can also lead to undesirable outcomes in the future, such as impoverishment of AIDS-affected households, higher antiretroviral drug-resistance rates and greater need for complex, expensive second-line antiretroviral drugs.

**Editors' note: Using data demonstrating that, for many people on HIV treatment in China, out-of-pocket expenditures reach 'catastrophic' health expenditure levels, the authors urge policy makers to consider both patient health and long-term treatment programme viability in designing strategies to prevent widespread resistance. Out-of-pocket expenditures create serious impediments for people who need antiretroviral therapy to access treatment, attend clinic regularly, and achieve high adherence levels. There are cogent economic arguments in favour of a free minimum package of HIV care that goes beyond antiretroviral drugs to include HIV tests, consultations, laboratory testing, hospitalisation, prophylaxis, and treatment of common opportunistic infections.**

Alkenbrack Batteh SE, Forsythe S, Martin G, Chettra T. Confirming the impact of HIV/AIDS epidemics on household vulnerability in Asia: the case of Cambodia. *AIDS*. 2008;22 Suppl 1:S103-11.

This study explores the effects of HIV on household economics and the social wellbeing of children in HIV-affected families in Cambodia. A purposive sample of parents living with HIV and their children was selected from networks of people living with HIV. Nearest-

neighbour' households served as the comparison group. Interviews were conducted with the parent and at least one child or adolescent in each household between October 2003 and January 2004. The urban/rural sample included 1000 households, 1000 adults, and 1443 children aged 6-17 years, inclusive, and was drawn from Phnom Penh, Battambang and Takeo provinces. Despite similar overall expenditures, HIV-affected households incurred proportionately larger expenditures on medical care and funerals. Income among case households was lower than comparison households. HIV-affected households were more likely to sell off assets, borrow from family members, take out loans, and ration medical care and food for children. Children in HIV-affected households reported eating fewer meals in a day, increased frequency of hunger, and increased household and employment responsibilities compared with comparison children. School enrollment rates were similar between pairs of households. The results add to growing evidence that HIV contributes to increased vulnerability to poverty and increased burdens on families and children. This study corroborates findings from previous studies in Asia, while providing country-specific information to stakeholders in Cambodia. At this stage in the epidemic, policy makers should focus on implementing and evaluating mitigation interventions. **Editors' note: Using a 'nearest neighbour' comparison group to try to disentangle risk from impact (HIV and poverty are known to influence each other with HIV exacerbating poverty and poverty increasing HIV exposure risk), this large study confirms the dis-saving associated with HIV-related illnesses. Economic survival strategies come at the expense of longer-term investments in the household affecting future generations. Children in HIV-affected households are significantly disadvantaged compared to their neighbouring peers despite the food assistance provided to 81% of the case households. Implementation and evaluation of comprehensive mitigation strategies are urgently needed to inform policymaking and minimise the long-term impacts of HIV on low-income countries such as Cambodia.**

#### **4. Tuberculosis**

Grandjean L, Moore DA Tuberculosis in the developing world: recent advances in diagnosis with special consideration of extensively drug-resistant tuberculosis. *Curr Opin Infect Dis.* 2008;21(5):454-61.

Globally tuberculosis is mainly diagnosed by sputum smear microscopy, which fails to detect half of all cases and fails to identify drug resistance. Inadequate global tuberculosis control through the directly observed therapy short course strategy alone and the growing threat of multidrug-resistant and extensively drug-resistant tuberculosis has driven recent development of new commercial and noncommercial tests, which are most desperately needed in resource-limited, high-burden settings. This review outlines the range of options currently available, highlighting particularly those recent developments with greatest potential for addressing the growing multidrug-resistant and extensively drug-resistant disaster as it affects those communities least technically and financially capable of controlling it. Simplification of molecular-diagnostic techniques, rapid-liquid culture and the use of colorimetric indicators have improved the sensitivity, speed and reliability of tuberculosis and multidrug-resistant tuberculosis detection, while decreasing cost and bringing diagnosis closer towards (though still some way from) the point-of-care. Global tuberculosis control in 2008 demands the use of new tools for more sensitive and rapid detection of active disease and of drug resistance. Improved technologies are available for reference laboratories but for settings where resources and technical capacity are limited

there is little ready for field implementation. The pipeline is promising, but in the interim wider use of liquid culture and manual or colorimetric drug susceptibility testing should be promoted. **Editors' note: In high-disease burden resource-constrained settings, sustainable human resources, sample transport, biosafety, and laboratory maintenance are as important as having a good test. In this era of MDRTB and XDRTB (multi- and extensively- drug-resistant TB), rational decision-making on implementation and long-term feasibility requires conducting formal evaluations of the cost-effectiveness of new and existing tests, including century-old sputum microscopy.**

Nuttall JJ, Davies MA, Hussey GD, Eley BS. Bacillus Calmette-Guérin (BCG) vaccine-induced complications in children treated with highly active antiretroviral therapy. *Int J Infect Dis.* 2008;12(6):e99-e105

Nuttall and colleagues aimed to describe the frequency, risk factors, and clinical features of bacillus Calmette-Guérin (BCG) complications in HIV-infected children treated with highly active antiretroviral therapy (HAART). A retrospective study of children started on HAART between August 2002 and November 2004 was completed. Six percent (21/352; 95% CI 3.7-8.0%) developed BCG complications. All developed ipsilateral axillary lymphadenitis; one child had suspected disseminated BCG infection. There were 14 females; median age at start of HAART was 5 months. BCG disease developed a median of 34 days after starting HAART. At baseline and 6 months into HAART, the median CD4 percentage and log(10) viral load were 12.3/6.1 and 23.9/4.5, respectively. Seventeen (81%) of the patients were treated with either zidovudine or stavudine combined with lamivudine and ritonavir. Young age and high baseline viral load were independent risk factors for development of BCG complications. Mycobacterium bovis BCG was isolated in 70% of patients who underwent incision and drainage of abscesses at the vaccination site or regional lymph nodes. This study identified a high prevalence of BCG complications in children on HAART. A clinical case definition of BCG immune reconstitution syndrome independent of laboratory parameters for use in resource-limited settings should be developed. **Editors' note: This South African study suggests that infants and children with HIV infection who have received the bacillus Calmette-Guerin (BCG) vaccine, a routine immunisation at birth in high TB-burden settings, should be monitored closely for BCG complications during the first 3 to 6 months of antiretroviral treatment. These complications seem to be manifestations of immune reconstitution inflammatory syndrome (IRIS) provoked by restoration of pathogen-specific immune responses as the immune system begins to recover following treatment initiation. In light of the risk of IRIS, BCG vaccine should be withheld when the mother's HIV-positive status is known, until the HIV-negative status of the infant has been established.**

## **5. Intimate Partner Violence**

Gupta J, Silverman JG, Hemenway D, Acevedo-Garcia D, Stein DJ, Williams DR. Physical violence against intimate partners and related exposures to violence among South African men. *CMAJ.* 2008;179(6):535-41.

Despite high rates of intimate partner violence in South Africa, there have been no national studies of men's perpetration of violence against female partners. Gupta and colleagues analyzed data from the South Africa Stress and Health Study, a cross-sectional, nationally representative study, specifically examining data for men who had ever been married or had ever cohabited with a female partner. They calculated the prevalence of physical violence

against intimate female partners and used logistic regression to examine associations with physical abuse during childhood and exposure to parental and community violence. A total of 834 male participants in the South Africa Stress and Health Study met the study criteria. Of these, 27.5% reported using physical violence against their current or most recent female partner during their current or most recent marriage or cohabiting relationship. Crude odds ratios (ORs) and 95% confidence intervals (CIs) indicated significant associations between perpetration of violence against an intimate partner and witnessing parental violence (OR 3.91, 95% CI 2.66-5.73) or experiencing physical abuse during childhood (OR 3.24, 95% CI 2.27-4.63), but not exposure to community violence (OR 1.29, 95% CI 0.88-1.88). The 2 significant associations persisted in adjusted analyses: OR 3.22 (95% CI 1.94-5.33) for witnessing parental violence and OR 1.73 (95% CI 1.07-2.79) for experiencing physical abuse during childhood. The authors concluded that they had found a high prevalence of physical violence perpetrated by men against their intimate partners. Men who experienced physical abuse during childhood or were exposed to parental violence were at the greatest risk.

**Editors' note: More than a quarter of men in this nationally representative study reported having perpetrated physical violence against their most recent partner. The estimate would likely have been higher if the question had been about lifetime perpetration of violence against all intimate partners. This behaviour was more prevalent in men who were abused themselves as children or who had witnessed parental violence. In both cases, this may have led them to view such behaviour as normative. Intimate partner violence, sexually risky behaviours, and HIV infection are interlinked making condemnation of intimate partner violence both an HIV prevention and human rights imperative.**

Le Cœur S, Khat M, Halembokaka G. Increased HIV infection rate among violent deaths: a mortuary study in the Republic of Congo. *AIDS*. 2008;22(13):1675-6.

There is no evidence to suggest an association between violent deaths and HIV in Africa. Le Cœur and colleagues report the results of a study performed in Pointe-Noire, Congo, where post-mortem HIV serologies were performed among all deaths referred to the morgue. The HIV prevalence among violent deaths was 37%, significantly higher than 10% among accidental deaths, with an adjusted odds ratio of 6 (P = 0.03). Prevention of domestic violence and fight against stigmatization should be parts of HIV programmes in Africa.

**Editors' note: To obtain a death certificate for burial in Pointe-Noire, the bodies of all deceased persons must be taken to the city morgue, making for a relatively complete denominator. Of the 1309 deaths registered during the study period, 14 were homicides and 5 suicides. More than a third of these people were HIV-positive at the time of death. Of the 4 HIV-positive homicides, 3 were women who had been slaughtered by a family member. These small but striking numbers highlight the importance of fighting stigma and preventing domestic violence.**

## 6. Treatment

Gupta R, Hill A, Sawyer AW, Pillay D. Emergence of drug resistance in HIV type 1-infected patients after receipt of first-line highly active antiretroviral therapy: a systematic review of clinical trials. *Clin Infect Dis*. 2008;47(5):712-22.

Resistance to antiretroviral combination therapy is associated with increased mortality. Understanding the relative risks of emerging resistance to first-line therapy is of

importance for both resource-rich and resource-poor settings. Gupta and colleagues undertook an overview of clinical trials of adults receiving first-line highly active antiretroviral therapy, which consisted of dual nucleoside reverse-transcriptase inhibitors (NRTIs) combined with a third agent (either a nonnucleoside reverse-transcriptase inhibitor [NNRTI] or a ritonavir-boosted protease inhibitor [bPI]). The primary outcome measures were incidences of mutations conferring resistance to key drugs (NRTIs, NNRTIs, or bPIs) per trial at week 48. For meta-analysis, inverse-variance weighting was used to create estimates of overall incidences per group, with exact 95% confidence intervals (95% CIs). The study included 20 clinical trials that comprised 30 treatment arms and 7970 patients. Virologic failure at 48 weeks occurred in 4.9% (95% CI, 3.9%-6.1%) of NNRTI recipients, compared with 5.3% (95% CI, 4.4%-6.4%;  $P = .50$ ) of bPI recipients. Of failures that were successfully genotyped, the M184V mutation in the HIV reverse transcriptase (lamivudine resistance) occurred in 35.3% (95% CI, 29.3%-41.6%) of patients who started NNRTI-based HAART, compared with 21.0% (95% CI, 14.4%-28.8%;  $P < .001$ ) for those who received a bPI. For the K65R mutation in the HIV reverse transcriptase (multinucleoside resistance), incidences were 5.3% (95% CI, 2.4%-9.9%) and 0.0% (95% CI, 0.0%-3.6%;  $P = .01$ ), respectively, in patients treated with non-zidovudine-containing regimens. Resistance to the third agent (an NNRTI or PI) occurred in 53% (95% CI, 46%-60%) and 0.9% (95% CI, 0.0%-6.2%;  $P < .001$ ) of such patients, respectively. Initial therapy with ritonavir-boosted protease inhibitor-based regimens resulted in less resistance within and across drug classes. This finding is of particular significance for the developing world, where rates of resistance to NRTIs and NNRTIs at 48 weeks are much higher than has been seen in both cohorts and clinical trials in well-resourced countries. **Editors' note: Co-formulation, simplicity of administration, price, drug interactions (particularly with TB therapy), toxicity, adverse events, and resistance at failure are among the factors to consider when choosing an initial antiretroviral regimen. Nonetheless, with virological failure rates almost double in resource-constrained settings, possibly because less-intensive virological monitoring leads to unrecognised prolonged viraemia, the results of this standardized meta-analysis of clinical trials do give pause for reflection. Of the two first line strategies recommended by WHO - 2 NRTIs plus either an NNRTI or a boosted PI - the latter wins the day on the resistance scale. Minimising drug resistance limits transmission of drug-resistant viruses and keeps treatment options open when virus rebounds on first line treatment.**

Willig JH, Abrams S, Westfall AO, Routman J, Adusumilli S, Varshney M, Allison J, Chatham A, Raper JL, Kaslow RA, Saag MS, Mugavero MJ. Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy. *AIDS*. 2008;22(15):1951-60.

Data on initial antiretroviral regimen longevity predates the arrival of newer nucleoside reverse transcriptase inhibitor backbones and once-daily regimens. Modern regimens are thought to possess greater tolerability and convenience. Willig et al hypothesized this would translate into greater durability. A retrospective study of antiretroviral-naïve patients starting treatment at the University of Alabama at Birmingham 1917 HIV/AIDS Clinic 1 January 2000-31 July 2007 was conducted. Two periods of antiretroviral initiation were identified, prior and after August 2004 (arrival of once-daily fixed-dose regimens). Kaplan-Meier survival analyses of regimen durability by time period and regimen characteristics were performed. Staged Cox proportional hazards models evaluated the roles of dosing complexity and composition in explaining differences in regimen durability between study

periods. Overall 542 patients started antiretroviral drugs (n = 309, January 2000-July 2004; n = 233, August 2004-July 2007). Median durability was 263 days longer in after August 2004 regimens. Regimens started before August 2004 had increased hazards for discontinuation relative to after August 2004 regimens [hazard ratio (HR) = 1.44; 95% confidence interval (CI) = 1.03-2.02]. Time period of initiation lost statistical significance when the model included dosing frequency (HR = 1.92 for at least twice daily vs. daily; 95% CI = 1.29-2.88). As regimen composition variables were added, time period and dosing frequency lost significance. Increased hazards of discontinuation were observed with didanosine or stavudine relative to abacavir or tenofovir use (HR = 1.92; 95% CI = 1.29-2.88) and all third drugs compared with non-nucleoside reverse transcriptase inhibitor-based regimens (triple-nucleoside reverse transcriptase inhibitor HR = 1.76; 95% CI = 1.14-2.73; unboosted-protease inhibitor HR = 1.58; 95% CI = 1.02-2.46; boosted-protease inhibitor HR = 1.57; 95% CI = 1.02-2.41). Affective mental health disorders increased the hazard of discontinuation in all models. Durability of contemporary once-daily fixed-dose antiretroviral regimens has significantly eclipsed the duration of earlier antiretroviral drug options. Our results indicate this is due to both more convenient dosing and improved tolerability of modern antiretroviral regimens. **Editors' note: Prolonging antiretroviral regimen durability, key to achieving long-term treatment success, starts with preserving the first line as long as possible. This study of treatment-naïve patients starting on antiretroviral therapy in one US centre underscores the dramatic impact that co-formulated fixed-dose regimens and improved tolerability have on the durability of first line regimens, even in a population in which 45% of patients had diagnosed affective disorders known to potentially affect adherence.**

## 7. HIV Testing

Mkwanazi NB, Patel D, Newell ML, Rollins NC, Coutsooudis A, Coovadia HM, Bland RM. Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Durban, South Africa. Rapid testing may not improve uptake of HIV testing and same day results in a rural South African community: a cohort study of 12,000 women. *PLoS ONE*. 2008;3(10):e3501.

Rapid testing of pregnant women aims to increase uptake of HIV testing and results and thus optimize care. Mkwanazi and colleagues report on the acceptability of HIV counselling and testing, and uptake of results, before and after the introduction of rapid testing in this area. HIV counsellors offered counselling and testing to women attending 8 antenatal clinics, prior to enrolment into a study examining infant feeding and postnatal HIV transmission. From August 2001 to April 2003, blood was sent for HIV ELISA testing in line with the Prevention of Mother-to-Child Transmission (PMTCT) programme in the district. From May 2003 to September 2004 women were offered a rapid HIV test as part of the PMTCT programme, but also continued to have ELISA testing for study purposes. Of 12,323 women counselled, 5,879 attended clinic prior to May 2003, and 6,444 after May 2003 when rapid testing was introduced; of whom 4,324 (74.6%) and 4,810 (74.6%) agreed to have an HIV test respectively. Of the 4,810 women who had a rapid HIV test, only 166 (3.4%) requested to receive their results on the same day as testing, the remainder opted to return for results at a later appointment. Women with secondary school education were less likely to agree to testing than those with no education (adjusted odds ratio 0.648, p<0.001), as were women aged 21-35 (adjusted odds ratio 0.762, p<0.001) and >35 years (adjusted odds ratio 0.756, p<0.01) compared to those <20 years. Contrary to other reports, few women who had rapid tests accepted their HIV results the same day. Finding strategies to increase the

proportion of pregnant women knowing their HIV results is critical so that appropriate care can be given. **Editors' note: Rapid HIV testing avoids transportation of samples to laboratories and ensures that women presenting late in pregnancy can receive their results prior to labour and delivery. This study of rapid testing among pregnant women attending clinics that offered HIV testing from 2001 as part of a postnatal transmission study, found little interest in the same-day result that rapid testing allows. Rapid testing had no effect on the proportion of women agreeing to have an HIV test (about 75%). This could be due to women wanting time to consider their personal risks and support networks before accepting results. It is important to respect pregnant women's abilities and readiness to receive HIV test results. Community mobilisation for stigma reduction and serostatus knowledge may work better than a technological advancement to increase the proportion of women who know their HIV status in pregnancy. Only then will the current unacceptable rates of mother-to-child transmission decrease and will more eligible women get on antiretroviral drugs for their own health.**

## **8. Injecting Drug Use**

Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, Wodak A, Panda S, Tyndall M, Toufik A, Mattick RP; for the 2007 Reference Group to the UN on HIV and Injecting Drug Use. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet*. 2008;372(9651):1733-45.

Injecting drug use is an increasingly important cause of HIV transmission in most countries worldwide. Mathers and colleagues set out to determine the prevalence of injecting drug use among individuals aged 15-64 years, and of HIV among people who inject drugs. They did a systematic search of peer-reviewed (Medline, EmBase, and PubMed/BioMed Central), internet, and grey literature databases; and data requests were made to UN agencies and international experts. 11 022 documents were reviewed, graded, and catalogued by the Reference Group to the UN on HIV and Injecting Drug Use. Injecting drug use was identified in 148 countries; data for the extent of injecting drug use was absent for many countries in Africa, the Middle East, and Latin America. The presence of HIV infection among injectors had been reported in 120 of these countries. Prevalence estimates of injecting drug use could be ascertained for 61 countries, containing 77% of the world's total population aged 15-64 years. Extrapolated estimates suggest that 15.9 million (range 11.0-21.2 million) people might inject drugs worldwide; the largest numbers of injectors were found in China, the USA, and Russia, where mid-estimates of HIV prevalence among injectors were 12%, 16%, and 37%, respectively. HIV prevalence among injecting drug users was 20-40% in five countries and over 40% in nine. Worldwide, an estimated 3.0 million (range 0.8-6.6 million) people who inject drugs might be HIV positive. The number of countries in which the injection of drugs has been reported has increased over the last decade. The high prevalence of HIV among many populations of injecting drug users represents a substantial global health challenge. However, existing data are far from adequate, in both quality and quantity, particularly in view of the increasing importance of injecting drug use as a mode of HIV transmission in many regions. **Editors' note: This systematic assessment of peer-reviewed and grey (non-peer-reviewed) literature by the 2007 Reference Group to the UN on HIV and Injecting Drug Use found that injecting drug use is occurring in 148 countries of the world of which 128 have reported HIV infection in this population, an apparent rise since the last such study published in 2004. Inadequate investment in**

research to document HIV prevalence and to evaluate HIV prevention programmes with a view to improving performance is hampering evidence-informed decision-making to minimise harms. Enough is known already about HIV prevention, as well as treatment and care of HIV-positive injecting drug users, for effective action. It is important to study local impact so that strategies can be adjusted for optimum results.

## 9. *Epidemiology*

Leclerc PM, Garenne M. Commercial sex and HIV transmission in mature epidemics: a study of five African countries. *Int J STD AIDS*. 2008;19(10):660-4.

The study compares the association between using the services of commercial sex workers and male HIV seroprevalence in five African countries: Ghana, Kenya, Lesotho, Malawi and Rwanda. The HIV seroprevalence among men who 'ever paid for sex' was compared with controls who 'never paid for sex'. Results were based on 12,929 eligible men, aged 15-59 years, interviewed in Demographic and Health Surveys. The odds ratio of HIV seroprevalence associated with ever paying for sex was 1.89 (95% confidence interval = 1.57-2.28), with only minor differences by country. The results were stable in multivariate analysis after controlling for available potential cofactors (data on non-sexual routes of transmission were not available). Given the relatively small proportion of men involved, the risk attributable to 'ever paying for sex' remained low: 7.1% in univariate analysis and 4.4% after adjustment, and it varied among countries (range 1.3-9.4%). These results match previous observations that commercial sex seems to play a minor role in the spread of HIV in mature epidemics. **Editors' note: Commercial sex clearly was a main source of HIV transmission in the mid-1980s in sub-Saharan Africa's heterosexual epidemics, creating an imbalance between the sexes with larger numbers of men infected and dying of AIDS than women. The situation is much changed in the mature HIV epidemics of today, with a balance between the sexes or even more women than men infected and commercial sex playing a minor role in epidemic dynamics. Nevertheless, programmes to reduce HIV transmission between sex workers and their clients in sub-Saharan Africa can still benefit the whole population and should be strengthened.**

## 10. *Faith-based organisations*

Rankin SH, Lindgren T, Kools SM, Schell E. The condom divide: disenfranchisement of Malawi women by church and state. *J Obstet Gynecol Neonatal Nurs*. 2008;37(5):596-604; quiz 604-6.

Rankin and colleagues examined the impact of 2 mitigating social institutions, religious organizations, and the state, on Malawi women's vulnerability to HIV. In-depth interviews with a purposive sample of 40 central leaders from 5 faith-based organizations in Malawi were recorded and transcribed as part of an on-going larger study. Qualitative description was used to identify themes and categories. The study took place in primarily urban and periurban areas of south-central Malawi. A minimum of 6 leaders from each faith-based organization were interviewed; the mean age of the primarily male (68%) participants was 44 years (range 26-74). Analysis of religious leaders' messages about HIV produced an overarching theme, the condom divide, which conceptualized the divergence between faith-based organizations and the state's prevention messages related to HIV prevention strategies. The authors conclude that faith-based organizations have « demonized » state messages about condoms as promoting sin. The faith-based organizations' insistence on abstinence and faithfulness leaves women with few options to protect themselves. As socially

conscious citizens of the world, nurses can increase the responsiveness to the disparate levels of suffering and death in countries like Malawi. **Editors' note: Whereas the Malawi government has broken the silence about sexual behaviours and their contributions to the HIV epidemic and is actively involved in HIV prevention, faith-based organisations in this country in which religion plays an important role are lagging behind. About 55% of the population is Protestant, 20% Catholic, and 15% Muslim, while 10% practice African traditional religions. This study of 40 religious leaders representing 5 faith-based organisations (3 mainstream Christian, 1 indigenous Pentecostal, and 1 Muslim) revealed that religious leaders, who are uniquely positioned to champion HIV prevention across Malawi, have largely refused or been reluctant to do so. Condoms are condemned except for discordant couples and there is little acknowledgement that the disadvantaged position of women along with double standards for sexual behaviour place women at heightened risk of HIV exposure. A human rights-public health approach that respects the right of everyone to sound scientific evidence to preserve health and encourages everyone to act responsibly would be a synergistic contribution that religious organisations could make now to the AIDS response in Malawi.**

### 11. Pathogenesis

Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, Ledergerber B, Lundgren J, Neuhaus J, Nixon D, Paton NI, Neaton JD; INSIGHT SMART Study Group Inflammatory and coagulation biomarkers and mortality in patients with HIV infection.. *PLoS Med.* 2008;5(10):e203.

In the Strategies for Management of Anti-Retroviral Therapy trial, all-cause mortality was higher for participants randomized to intermittent, CD4-guided antiretroviral treatment (drug conservation [DC]) than continuous antiretroviral treatment (viral suppression [VS]). Kuller et al hypothesized that increased HIV-RNA levels following antiretroviral treatment interruption induced activation of tissue factor pathways, thrombosis, and fibrinolysis. Stored samples were used to measure six biomarkers: high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), amyloid A, amyloid P, D-dimer, and prothrombin fragment 1+2. Two studies were conducted: (1) a nested case-control study for studying biomarker associations with mortality, and (2) a study to compare participants in the drug conservation and viral suppression trial arms for biomarker changes. For (1), markers were determined at study entry and before death (latest level) for 85 deaths and for two controls (n = 170) matched on country, age, sex, and date of randomization. Odds ratios (ORs) were estimated with logistic regression. For each biomarker, each of the three upper quartiles was compared to the lowest quartile. For (2), the biomarkers were assessed for 249 drug conservation and 250 viral suppression participants at study entry and 1 month following randomization. Higher levels of high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and D-dimer at study entry were significantly associated with an increased risk of all-cause mortality. Unadjusted ORs (highest versus lowest quartile) were 2.0 (95% confidence interval [CI], 1.0-4.1; p = 0.05), 8.3 (95% CI, 3.3-20.8; p < 0.0001), and 12.4 (95% CI, 4.2-37.0; p < 0.0001), respectively. Associations were significant after adjustment, when the drug conservation and viral suppression groups were analyzed separately, and when latest levels were assessed. IL-6 and D-dimer increased at 1 month by 30% and 16% in the drug conservation group and by 0% and 5% in the viral suppression group (p < 0.0001 for treatment difference for both biomarkers); increases in the drug conservation group were related to HIV-RNA levels at 1 month (p < 0.0001). In an expanded case-control analysis (four controls per case), the odds

ratio (drug conservation/viral suppression) for mortality was reduced from 1.8 (95% CI, 1.1-3.1; p = 0.02) to 1.5 (95% CI, 0.8-2.8) and 1.4 (95% CI, 0.8-2.5) after adjustment for latest levels of IL-6 and D-dimer, respectively. The authors conclude that IL-6 and D-dimer were strongly related to all-cause mortality. Interrupting ART may further increase the risk of death by raising IL-6 and D-dimer levels. Therapies that reduce the inflammatory response to HIV and decrease IL-6 and D-dimer levels may warrant investigation. **Editors' note:**

**Confidence intervals for the odd ratios in this analysis are wide, due to the low number of deaths in the SMART study which enrolled relatively health people living with HIV, and they lose statistical significance in the expanded case-control analysis. In any case most deaths were not HIV-related. Increases in inflammatory markers from the first study visit to the study preceding death appear to be associated with increased risk of death and several were more commonly found in people in the treatment interruption arm. HIV induces activation of inflammatory and coagulation pathways and it is these inflammatory changes that may be associated with premature mortality in people living with HIV. It should be recalled however that biomarker levels just before death may reflect reverse causality - they may be the result of an already present disease process rather than causing it. More research is needed.**

Cadogan M, Dalgleish AG. HIV immunopathogenesis and strategies for intervention. *Lancet Infect Dis.* 2008;8(11):675-84

Therapeutic options aimed at tackling the HIV pandemic face many obstacles. The lack of readily accessible and affordable therapies means that most of those affected go untreated. The array of escape mechanisms used by HIV has undermined the efficiency of many antiviral products and continually represents a barrier to the development of an effective vaccine. Recent developments have seen a shift away from a cytopathic viral model of HIV pathogenesis towards the crucial role of immunopathogenic features-notably generalised immune activation-in the development of AIDS. As conventional vaccine strategies have sought to promote viral neutralisation and suppressive cellular responses, novel strategies that aim to address HIV immunopathogenesis should be sought. We review current opinion on HIV-induced pathogenic immune activation and strategies aimed at eliminating HIV, including a potential role for non-neutralising antibodies as part of a therapeutic vaccine option.

**Editors' note: Current HIV treatment focuses on interrupting the viral life-cycle using long-term reduction of viral load as a measure of success. Despite complete viral suppression, chronic generalised immune activation can persist with resultant progression to AIDS. Although HIV is well adapted to humans, taking advantage of cellular machinery for replication and transmission while using a number of immune evasion strategies, it provokes immune activation. This inadvertently benefits HIV because activated lymphocytes are its preferential targets. After reading this review, which has good tables and coloured graphics of virus-lymphocyte interactions, you will be hard pressed not to be convinced that more effort should be devoted to understanding and minimising HIV immunopathogenesis.**

## 12. Microbicides

Smith DJ, Wakasiaka S, Hoang TD, Bwayo JJ, Del Rio C, Priddy FH. An evaluation of intravaginal rings as a potential HIV prevention device in urban Kenya: behaviors and attitudes that might influence uptake within a high-risk population. *J Womens Health (Larchmt).* 2008;17(6):1025-34.

Smith and colleagues sought to assess the potential acceptability of intravaginal rings as an HIV prevention method among at-risk women and men. They conducted a qualitative assessment of initial attitudes toward intravaginal rings, current HIV prevention methods, and common behavioural practices among female sex workers and men who frequent them in Mukuru, an urban slum community in Nairobi, Kenya. Nineteen women and 21 men took part in six focus group discussions. Most participants, both male and female, responded positively to the concept of an intravaginal ring as a device for delivering microbicides. Women particularly liked the convenience offered by its slow-release capacity. Some female respondents raised concerns about whether male customers would discover the ring and respond negatively, whereas others thought it unlikely that their clients would feel the ring. Focus groups conducted with male clients of sex workers suggested that many would be enthusiastic about women, and particularly sex workers, using a microbicide ring, but that women's fears about negative responses to covert use were well founded. Overall, this high-risk population of female sex workers and male clients in Nairobi was very open to the intravaginal ring as a potential HIV prevention device. Themes that emerged from the focus groups highlight the importance of understanding attitudes toward intravaginal rings as well as cultural practices that may affect intravaginal ring use in high-risk populations when pursuing clinical development of this potential HIV prevention device. **Editors' note: Intravaginal rings, developed to deliver hormones for contraception and hormone replacement therapy, have been found acceptable in 3 high-income country studies. This is the first study to look at intravaginal ring acceptability in a low- or middle-income country and the first to specifically address the subject of intravaginal rings for microbicide delivery to prevent HIV infection. These flexible silicone rings 2 to 3 inches in diameter are designed to be inserted in the vagina and placed near the cervix for 3 to 12 months to provide a more steady flow of microbicide than the coitally-dependent topical gels, films, or suppositories that require adherence. This study of sex workers and their clients found high levels of acceptability but concerns about covert use. Men voiced a strong belief that they have the right to be informed should any sexual partner use a vaginal ring and that they would not pay or would respond with anger should they discover that a sex worker was using a ring without their consent. If eventual trials of microbicides using this delivery system have positive results, more work on the positioning of the product will be needed to increase understanding and encourage acceptability on all sides.**

Wu L. Biology of HIV Mucosal Transmission. *Curr Opin HIV AIDS*. 2008;3(5):534-540.

HIV-1 mucosal transmission plays a critical role in HIV-1 infection and AIDS pathogenesis. This review summarizes the latest advances in biological studies of HIV-1 mucosal transmission, highlighting the implications of these studies in the development of microbicides to prevent HIV-1 transmission. New studies of initial HIV-1 infection using improved culture models updated the current view of mucosal transmission. Mechanistic studies enhanced our understanding of cell-cell transmission of HIV-1 mediated by the major target cells, including dendritic cells, CD4(+) T cells, and macrophages. Increasing evidence

indicated the significance of host factors and immune responses in HIV-1 mucosal infection and transmission. Recent progress in HIV-1 mucosal infection and transmission enriches our knowledge of virus-host interactions and viral pathogenesis. Functional studies of HIV-1 interactions with host cells can provide new insights into the design of more effective approaches to combat HIV-1 infection and AIDS. **Editors' note: Since the mucosal route is the most common pathway for HIV transmission, the development of targeted prevention and treatment strategies requires improved understanding of how HIV penetrates the mucosa to establish infection. This review focuses on cell-cell transmission of HIV, highlighting the role of dendritic cells, CD4 T cells, and macrophages, along with the host factors influencing mucosal transmission. This is the biology we need to know to design effective microbicides, antiretroviral drugs, and vaccines.**

### **13. Prevention trial conduct**

Bull SS, Vallejos D, Levine D, Ortiz C. Improving recruitment and retention for an online randomized controlled trial: experience from the Youthnet study. *AIDS Care*. 2008;20(8):887-93.

The objective of the study was to present recruitment and retention findings for an Internet based HIV prevention trial evaluated using a randomized controlled design among 15-25-year-olds accessing a website on the Internet. Bull and colleagues used a combination of automated electronic and personalized approaches to increase and diversify recruitment, verify participant eligibility and increase retention. They posted 3.5 million banner advertisements, 9354 individuals clicked on the advertisement, 8950 completed an eligibility screener and 3298 a baseline survey; they flagged 675 of these as suspicious and enrolled 2623 individuals. Of these, 2082 (79%) completed a follow-up at one-month and 1398 (53%) completed a two-month follow-up. This retention rate is the highest seen for an Internet-based HIV-prevention trial. Their procedures can be replicated in other trials. We stress the importance of using a combination of automated and personalized techniques to increase enrollment, verify eligibility, and promote retention. **Editors' note: This report of on-line internet prevention trial conduct describes methodological challenges in recruiting and retaining diverse and uniquely-identified participants and ways of addressing these hurdles. The intervention itself *Keep it Real*, following a baseline risk assessment, exposed participants to multiple 20-30 second role model stories with models tailored to participant gender and race/ethnicity (intervention arm) or text-based generic HIV prevention information (control arm). Although the results are not presented here, this article on online research makes for interesting reading on research techniques in this increasingly virtual world of information.**

### **14. Youth**

McManus A, Dhar L. Study of knowledge, perception and attitude of adolescent girls towards STIs/HIV, safer sex and sex education: (a cross sectional survey of urban adolescent school girls in South Delhi, India). *BMC Womens Health*. 2008;8:12.

Sexually transmitted infections, including HIV mainly affect sexually active young people. Young adults aged 15-29 years, account for 32% of AIDS cases reported in India and the number of young women living with HIV is twice that of young men. The aim of the study was to evaluate adolescent school girls' knowledge, perceptions and attitudes towards STIs/HIV and safer sex practice and sex education and to explore their current sexual behaviour in

India. A cross sectional study was carried out in 2007 in South Delhi, India to investigate the perception, knowledge and attitude of adolescent urban schoolgirls towards sexually transmitted infections, HIV, safer sex practice, and sex education. The self-administered questionnaire was completed by 251 female students from two senior secondary schools. More than one third of students in this study had no accurate understanding about the signs and symptoms of sexually transmitted infections other than HIV. About 30% of respondents considered AIDS could be cured, 49% felt that condoms should not be available to youth, 41% were confused about whether the contraceptive pill could protect against HIV infection and 32% thought it should only be taken by married women. Though controversial, there is an immense need to implement gender-based sex education regarding sexually transmitted infections, safe sex options and contraceptives in schools in India. **Editors' note: The results of this survey of girls aged 14 to 19 years in two urban high schools in South Delhi are cause for concern. Sexually transmitted infections are second only to maternal morbidity and mortality as causes of death, illness, and 'years of healthy life lost' among women in their child-bearing years in India, as in other developing countries. Yet 71% had not heard of genital herpes and 44% and 43%, respectively, had not heard of gonorrhoea or syphilis. These findings, in addition to important gaps in HIV prevention knowledge and negative attitudes toward condoms and other safer sex strategies, pose major behaviour change and social change communication challenges. Young people need to be able to make informed choices about protecting themselves from sexually transmitted infection, including HIV, if or when they decide to become sexually active. India has work to do.**

That was *HIV this week*, signing off.

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