

HIV This Week: what scientific journals said

Welcome to the fifty-seventh issue of *HIV This Week*! In this issue, we cover **harm reduction** (HIV is spreading faster than the response - what should be done?; a Cochrane Review of substitution treatment for HIV prevention weighs in), **alcohol and HIV shedding** (why those extra drinks could matter), **helminth infection and HIV vulnerability** (fighting worms - will it ever join combination prevention in helminth endemic areas?), **paediatric treatment** (good but much more and much better needed in sub-Saharan Africa), **female-initiated methods** (one choice is no choice; microbicides, partial protection, and the prevention equation), **basic science** (another HIV reservoir - follicular dendritic cells; how your genes can affect treatment outcomes; can we block multiple steps of HIV replication?), **health care delivery** (where have all the patients gone 2 years after starting treatment in sub-Saharan Africa?; being a woman and having experienced providers predicts better treatment outcomes in Côte d'Ivoire), **male circumcision** (should we start measuring foreskin length in men?), **morbidity and co-morbidity** (all you want to know about kidney disease and HIV; how coinfection with herpes simplex virus type 2 activates the immune system and speeds HIV progression), **resilience** (constructive adaptation in the presence of adversity among young children whose mothers live with HIV), **national responses - strategic planning** (speed of scale-up and survival in South Africa), **treatment and care** (evolving disease patterns and patient profiles in France; integrase inhibitors for people with triple-class drug resistance), and **structural determinants** (sexual abuse rooted in historical trauma among young Aboriginal Canadians who use drugs).

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1. *Harm reduction*

Wodak A, McLeod L. The role of harm reduction in controlling HIV among injecting drug users. *AIDS*. 2008;Suppl 2:S81-92.

Injecting drug users now account for one in 10 new HIV infections world wide. Yet it has been known since the early 1990s that HIV among injecting drug users can be effectively, safely and cost-effectively controlled by the early and vigorous implementation of a

comprehensive package of strategies known as 'harm reduction'. This concept means that decreasing drug-related harms is accorded an even higher priority than reduction of drug consumption. Strategies required involve: explicit and peer-based education about the risk of HIV from sharing injecting equipment; needle syringe programmes; drug treatment (including especially opiate substitution treatment), and community development. Many countries experiencing or threatened by an HIV epidemic among injecting drug users have now adopted harm reduction but often implementation has been too little and too late. Although coverage is slowly improving in many countries, HIV is still spreading faster among injecting drug users than harm reduction programmes while coverage in correctional centres lags far behind community settings. The scientific debate about harm reduction is now over. National and international support for harm reduction is growing while almost all the major UN organizations responsible for drug policy now support harm reduction. Only a small number of countries, led by the USA, are still vehemently opposed to harm reduction. Excessive reliance on drug law enforcement remains the major barrier to increased adoption of harm reduction. Sometimes zealous drug law enforcement undermines harm reduction. A more balanced approach to drug law enforcement is required with illicit drug use recognized primarily as a health and social problem. **Editors' note: With injecting drug use reported from 144 countries, of which 128 have detected HIV among injecting drug users, the pragmatic approach of harm reduction must be scaled up deliberately and rapidly around the world. It is no longer conscionable to deny access to sterile needles and syringes or to substitution treatment for injecting drug users in the face of the evidence of the effectiveness of these programmes in reducing HIV infection. Promoting and protecting the human rights of injecting drug users underpin effective public health responses to stem the HIV epidemic among them. There is no time to lose.**

Gowing L, Farrell M, Bornemann R, Sullivan L, Ali R. Substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database Syst Rev.* 2008;(2):CD004145.

Injecting drug users are vulnerable to infection with HIV and other blood borne viruses as a result of collective use of injecting equipment as well as sexual behaviour. Gowing and co-authors aimed to assess the effect of oral substitution treatment for opioid-dependent injecting drug users on rates of HIV infections, and high risk behaviours. They searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and PsycINFO to March 2007. They also searched reference lists of articles, reviews, and conference abstracts. Studies were required to consider the incidence of risk behaviours, or the incidence of HIV infection related to substitution treatment of opioid dependence. All types of original studies were considered. Two reviewers independently assessed studies for inclusion. One reviewer extracted data from included studies, assessed quality, and confirmed decisions by consulting with all other reviewers. The authors included thirty-three studies, involving 10,400 participants. The majority were not randomised controlled studies and there were problems of confounding and bias. The studies varied in several aspects limiting the extent of quantitative analysis. Studies consistently showed that oral substitution treatment for opioid-dependent injecting drug users was associated with statistically significant reductions in illicit opioid use, injecting use, and sharing of injecting equipment. It was also associated with reductions in the proportion of injecting drug users reporting multiple sex partners or exchanges of sex for drugs or money, but had little effect on condom use. It appears that the reductions in risk behaviours related to drug use do translate into reductions in cases of HIV infection. The authors conclude that oral

substitution treatment for injecting opioid users reduces drug-related behaviours with a high risk of HIV transmission, but has less effect on sex-related risk behaviours. The lack of data from randomised controlled studies limits the strength of the evidence presented in this review. **Editors' note: This review assessing the effectiveness of oral substitution treatment in reducing injecting and sexual risk behaviours included studies of methadone, buprenorphine, LAAM (levo alpha acetyl methadol), codeine, and slow release morphine but not of the injectable preparations used in Switzerland, the Netherlands, the United Kingdom and Germany. Substitution treatment, a key pillar of harm reduction, reduces risk behaviours and HIV acquisition. It is high time to remove legal, policy, and other barriers to offering it to opioid dependent injecting drug users around the world who are ready to reduce or cease injecting illicit drugs.**

2. Alcohol and HIV shedding

Theall KP, Amedee A, Clark RA, Dumestre J, Kissinger P. Alcohol Consumption and HIV-1 Vaginal RNA Shedding Among Women. *J Stud Alcohol Drugs*. 2008;69(3):454-8.

The purpose of this study was to examine the association between alcohol consumption and HIV-1 vaginal shedding. HIV-1 infected women attending a large urban HIV primary care clinic in New Orleans, LA, between June 2002 and October 2004 who underwent a gynaecological exam, were 18 years of age or older, and provided informed consent were included. Subjects underwent exams and were interviewed using a computer-assisted survey at baseline, 1 month, and 3 months. Most of the women were black (86.4%), with a median age of 38 (range: 19-61 years). Most (56.7%) also were on antiretroviral therapy (with 89.6% self-reported adherence) and had a median CD4 of 404 copies/ml and a plasma viral load of 13,400 copies/ml at baseline. The overall period prevalence of vaginal shedding (>50 copies/swab) was 24.5%, with a baseline prevalence of 27.3%. At baseline, 30% reported any alcohol consumption, 32.6% were weekly drinkers, 25.5% were heavy episodic drinkers, and 10.0% had recent moderate to heavy alcohol consumption (two or more drinks the day before the interview). Recent moderate to heavy alcohol consumption and heavy episodic drinking were both strongly and positively associated with vaginal shedding but only among women on antiretroviral therapy. After adjusting for plasma viral load, immunosuppression, and antiretroviral therapy adherence, recent moderate to heavy alcohol consumption was significantly associated with vaginal shedding (adjusted prevalence odds ratio = 2.29, 95% confidence interval: 1.18-14.43). No association was observed for plasma viral load and alcohol consumption. Theall and colleagues concluded that recent alcohol consumption was associated with expression of HIV-1 RNA in vaginal fluids of women on antiretroviral therapy. Future research is needed to support this observation and to determine the mechanisms behind it. (*J. Stud. Alcohol Drugs* 69: 454-458, 2008). **Editors' note: This study's sample size was small (187 women) and women on antiretroviral treatment who were drinking were more likely to have a sexually transmitted infection, increasing the likelihood of genital tract HIV shedding. Although sexually transmitted infections were considered in the multivariate analysis, herpes simplex virus infection was not among them. Nonetheless, these findings are intriguing, particularly in the context of current discussions on the role of antiretroviral treatment in reducing onward HIV transmission.**

3. Helminth infection and HIV vulnerability

Chenine A-L, Shai-Kobiler E, Steele LN, Ong H, Augostini P, et al. Acute *Schistosoma mansoni* Infection Increases Susceptibility to Systemic SHIV Clade C Infection in Rhesus Macaques after Mucosal Virus Exposure. *PLoS Negl Trop Dis*. 2008;2(7):e265

Individuals living in sub-Saharan Africa represent 10% of the world's population but almost 2/3 of all people living with HIV. The disproportionate HIV-1 infection rates in this region may be linked to helminthic parasite infections that affect many individuals in the developing world. However, the hypothesis that parasite infection increases an individual's susceptibility to HIV-1 has never been prospectively tested in a relevant in vivo model. Chenine and colleagues measured whether pre-existing infection of rhesus monkeys with a parasitic worm would facilitate systemic infection after mucosal AIDS virus exposure. Two groups of animals, one consisting of normal monkeys and the other harbouring *Schistosoma mansoni*, were challenged intra-rectally with decreasing doses of R5-tropic clade C simian-human immunodeficiency virus (SHIV-C). Systemic infection occurred in parasitized monkeys at viral doses that remained sub-infectious in normal hosts. In fact, the 50% animal infectious (AID50) SHIV-C dose was 17-fold lower in parasitized animals compared to controls (P = 0.001). Coinfected animals also had significantly higher peak viral RNA loads than controls (P = 0.001), as well as increased viral replication in CD4+ central memory cells (P = 0.03). These data provide the first direct evidence that acute schistosomiasis significantly increases the risk of de novo HIV acquisition, and the magnitude of the effect suggests that control of helminth infections may be a useful public health intervention to help decrease the spread of HIV-1. **Editors' note: The possibility that helminth infections could be a risk factor for increased susceptibility to HIV infection among people living in areas endemic for these parasites has been raised for years. Macaques self cure their schistosomiasis 20 to 25 weeks after exposure to cercariae which limits the application of these findings to the acute phase of schistosomiasis. However, treatment of helminth infections is inexpensive, safe, and easily administered to communities. Important in its own sake, treatment of helminth infections in endemic areas should be further studied for its possible role in HIV prevention.**

4. Paediatric treatment

Sutcliffe CG, van Dijk JH, Bolton C, Persaud D, Moss WJ. Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. *Lancet Infect Dis*. 2008;8(8): 477-89.

Assessment of antiretroviral treatment programmes for HIV-infected children in sub-Saharan Africa is important to enable the development of effective care and improve treatment outcomes. Sutcliffe and colleagues review the effectiveness of paediatric antiretroviral treatment programmes in sub-Saharan Africa and discuss the implications of these findings for the care and treatment of HIV-infected children in this region. Available reports indicate that programmes in sub-Saharan Africa achieve treatment outcomes similar to those in North America and Europe. However, progress in several areas is required to improve the care of HIV-infected children in sub-Saharan Africa. The findings emphasise the need for low-cost diagnostic tests that allow for earlier identification of HIV infection in infants living in sub-Saharan Africa, improved access to antiretroviral treatment programmes, including expansion of care into rural areas, and the integration of antiretroviral treatment programmes with other health-care services, such as nutritional support. **Editors' note: Although this review of 30 sub-Saharan African paediatric**

studies in urban centres reveals early clinical, immunological, or virological outcomes and treatment adherence that are similar to those reported from high-income countries, there are concerns. At treatment entry, children are older (most are more than 5 years of age), more are immunosuppressed, and more are undernourished (more than half). Palatable, stable liquid preparations and fixed-dose antiretroviral combinations are not usually available and second-line regimens are costly (up to 59% of children had treatment failure or adverse reactions). Standardised monitoring and assessment systems are not in place and these are key to quality assurance as services expand to rural areas.

5. Female-initiated methods

Mantell JE, Stein ZA, Susser I. Women in the Time of AIDS: Barriers, Bargains, and Benefits. *AIDS Educ Prev.* 2008;(2):91-106.

Mantell and colleagues comment here on the implications of new HIV prevention technologies (physical and chemical barriers) for women's health and women's rights. Four relevant themes are selected that have emerged in the social and behavioural science literature: structural factors (global and national) limiting the availability of female condoms, control and empowerment with female-initiated HIV prevention technologies, covert use of female-initiated HIV prevention technologies, and male partners as part of the bargain for barriers. There is now a rich and diverse literature on all of these issues, relevant and informative, which the authors draw together in this commentary. Discussion of these themes suggests guidelines for policy, research, and action. First, the misconceptions, biases, and prejudices of global and national leaders, including donors, necessitate that we persevere in presenting data to them and engaging them in discussion. Second, we need to support women within their local social contexts to negotiate for their rights, balancing pragmatic approaches to their partners in their initiation of protection, and applying according to each situation as appropriate, a continuum from discretion and clandestine use to deception. Third, men have to be brought in as active participants, and their positive and negative experiences and interests inserted into practices and policies. **Editors' note: This thoughtful article underscores women's need for different HIV prevention methods at different life stages and with different partners. Subsidizing and scaling up female condom programming to overcome access and supply constraints and further trials of cervical barrier methods are urgently needed so that all women have an array of female-initiated protection methods to choose from.**

Hoffman S, Cooper D, Ramjee G, Higgins JA, Mantell JE. Microbicide acceptability: insights for future directions from providers and policy makers. *AIDS Educ Prev.* 2008;20(2):188-202.

To help fill the gap concerning health care providers' and policy makers' knowledge of and views concerning microbicides, Hoffman and colleagues compared data from one U.S. study and two South African studies that explored these issues. Frontline providers in South Africa were enthusiastic about any method that would have the potential to slow the HIV epidemic, whereas providers in New York City and policy makers in South Africa balanced their enthusiasm with more concerns. Across all studies, participants wanted timely and accurate scientific information, and they raised issues about safety, «messiness», and cost. Many had difficulty understanding that promoting a partially effective method can reduce risk if a client uses it more often than a highly effective method. Microbicide advocates need to effectively communicate to providers the evidence-based findings from microbicide

trials and find approaches to introduce concepts such as « harm reduction » and « prevention equation » perspectives in client counselling. Developing these approaches will maximize the positive influence that providers can exert on user acceptability of microbicides once they become available. **Editors' note: Discussions of partial protection and the prevention equation in relation to microbicides have resonance for other prevention methods, both currently available and under investigation. Health care providers who are skilled in explaining these concepts are crucial facilitators for the adoption of combination prevention for better protection.**

6. Basic science

Keele BF, Tazi L, Gartner S, Liu Y, Burgon TB, Estes JD, Thacker TC, Crandall KA, McArthur JC, Burton GF. Characterization of the Follicular Dendritic Cell Reservoir of HIV-1. *J Virol*. 2008 Apr 2 [Epub ahead of print]

Throughout the natural course of HIV infection, follicular dendritic cells trap and retain large quantities of particle-associated HIV RNA in the follicles of secondary lymphoid tissue. Keele and colleagues previously found that murine follicular dendritic cells in vivo could maintain trapped virus particles in an infectious state for at least 9 months. Here they sought to determine if human follicular dendritic cells serve as an HIV reservoir, based on the criteria that virus therein must be replication competent, genetically diverse and archival in nature. They tested their hypothesis using post-mortem cells and tissues obtained from three, HIV-infected subjects and ante-mortem blood samples obtained from one of them. Replication competence was determined using co-culture, while genetic diversity and the archival nature of virus were established using phylogenetic and population genetics methods. The authors found that follicular dendritic cell-trapped virus was replication-competent and demonstrated greater genetic diversity than that found in most other tissues and cells. Antiretroviral resistant variants were also detected on follicular dendritic cells that were not present elsewhere. Furthermore, genetic similarity was observed between follicular dendritic cell-trapped HIV and viral species recovered from peripheral blood mononuclear cells obtained 21 and 22 months ante-mortem, but not present in samples obtained 4 and 18 months prior to death, indicating that follicular dendritic cells can archive HIV. These data indicate that follicular dendritic cells represent a significant reservoir of infectious and diverse HIV thereby providing a mechanism for viral persistence for months to years. **Editors' note: It is believed that stable viral reservoirs established before the initiation of antiretroviral therapy are responsible for the low-level residual viraemia that can be detected with ultra sensitive assays in virtually all people living with HIV who have "undetectable" viral loads on standard assays. The genetic diversity of HIV found in follicular dendritic cells in this small post-mortem study suggests that these cells may be trapping HIV throughout the course of the disease; however, it is unclear whether this may be specific to individuals with worsening clinical prognosis and more frequent drug failures.**

Hendrickson SL, Jacobson LP, Nelson GW, Phair JP, Lautenberger J, Johnson RC, Kingsley L, Margolick JB, Detels R, Goedert JJ, O'Brien SJ. Host Genetic Influences on Highly Active Antiretroviral Therapy Efficacy and AIDS-Free Survival. *J Acquir Immune Defic Syndr*. 2008;48(3):263-71.

Hendrickson and colleagues studied the influence of AIDS-restriction genes (ARGs) CCR5-Delta32, CCR2-64I, SDF1-3' A, IL10-5' A, CX3CR1V249I, CX3CR1-T280M, and MDR1-

C3435T and haplotypes of the CCR5 P1 promoter and RANTES variants -403A, In1.1C, 3' 222C, and -28G among HIV-negative infected patients on highly active antiretroviral therapy in the Multicenter AIDS Cohort Study (MACS) and the Multicenter Hemophilia Cohort Study (MHCS). Their results indicate that several AIDS-restriction genes also influence therapy efficacy (ie, the success in viral suppression) and subsequent progression to AIDS while on highly active antiretroviral therapy. CCR5-Delta32 decreased time to viral suppression (<200 HIV RNA copies/mL, relative hazard [RH] = 1.40; P = 0.008) and was protective against AIDS (RH = 0.11; P = <0.0001), whereas the CCR5 P1 haplotype was associated with delayed viral suppression (RNA <50 copies/mL, odds ratio [OR] = 0.65; P = 0.03) and accelerated time to AIDS (RH = 2.68; P = 0.02). SDF1-3' A reduced viral suppression (OR = 0.61; P = 0.02) and accelerated AIDS (RH = 3.18; P = 0.009). Accelerated AIDS progression was also observed with the RANTES haplotype carrying RANTES-IN1.1C and RANTES-3' 222C (P = 0.005 to 0.007). In contrast, the RANTES haplotype H1, which lacks suspected deleterious single-nucleotide polymorphisms, was protective against AIDS. CX3CR1-V249I seemed to accelerate viral suppression (RNA <50 copies/mL, OR = 1.27; P = 0.01). AIDS-restriction gene influence after highly active antiretroviral therapy suggests residual HIV-1 replication, and spread continues even in patients successfully suppressing detectable viral RNA. **Editors' note: Host genetics likely play an important role in treatment success. AIDS restriction genes are genes with polymorphisms that influence HIV infection and AIDS progression in untreated patients, either positively or negatively. These are early days but it appears that genes involved with the CCR5 viral pathway are particularly important to treatment success.**

Readinger JA, Schiralli GM, Jiang JK, Thomas CJ, August A, Henderson AJ, Schwartzberg PL. Selective targeting of ITK blocks multiple steps of HIV replication. *Proc Natl Acad Sci U S A*. 2008;105(18):6684-9.

Treatment for HIV has relied on the use of antiretroviral agents that can be subject to the development of resistant viruses. The study of inhibitors directed against cellular proteins required for HIV replication is therefore of growing interest. Inducible T cell kinase (ITK) is a Tec family tyrosine kinase that regulates T cell receptor (TCR)-induced activation of PLCgamma-1, Ca(2+) mobilization and transcription factor activation, and actin rearrangement downstream of both TCR and chemokine receptors. Because productive infection of T cells with HIV requires T cell activation, chemokine receptors and actin reorganization, Readinger and colleagues asked whether ITK affects HIV infection using ITK-specific siRNA, a kinase-inactive ITK mutant or an ITK inhibitor. They demonstrate that loss of ITK function resulted in marked reductions in intracellular p24 levels upon HIV infection. Loss of ITK function after establishment of HIV infection also decreased virus spread within the culture. Inhibition of ITK did not affect expression of the HIV coreceptors CD4 or CXCR4 but partially blocked HIV viral entry, an effect that correlated with decreased actin polarization to gp120. Additionally, ITK was required for efficient HIV transcription, and over-expression of ITK increased both viral transcription and virus-like particle formation. The data suggest that inhibition of ITK blocks HIV infection by affecting multiple steps of HIV replication. **Editors' note: Inducible T cell kinase is a cellular protein that appears to regulate HIV replication, including viral entry, transcription, virion assembly, and release. Because it could affect multiple stages of the HIV replication life cycle, an inducible T cell kinase inhibitor could be an important addition to antiretroviral drug regimens.**

7. Health care delivery

Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. *PLoS Med.* 2007;4(10):e298.

Long-term retention of patients in Africa's rapidly expanding antiretroviral therapy programmes for HIV is essential for these programmes' success but has received relatively little attention. In this paper Rosen and colleagues present a systematic review of patient retention in antiretroviral therapy programmes in sub-Saharan Africa. They searched Medline, other literature databases, conference abstracts, publications archives, and the "grey literature" (project reports available online) between 2000 and 2007 for reports on the proportion of adult patients retained (i.e., remaining in care and on antiretroviral therapy) after 6 months or longer in sub-Saharan African, non-research antiretroviral therapy programs, with and without donor support. Estimated retention rates at 6, 12, and 24 months were calculated and plotted for each program. Retention was also estimated using Kaplan-Meier curves. In sensitivity analyses the authors considered best-case, worst-case, and midpoint scenarios for retention at 2 years; the best-case scenario assumed no further attrition beyond that reported, while the worst-case scenario assumed that attrition would continue in a linear fashion. The authors reviewed 32 publications reporting on 33 patient cohorts (74,192 patients, 13 countries). For all studies, the weighted average follow-up period reported was 9.9 months, after which 77.5% of patients were retained. Loss to follow-up and death accounted for 56% and 40% of attrition, respectively. Weighted mean retention rates as reported were 79.1%, 75.0% and 61.6% at 6, 12, and 24 months, respectively. Of those reporting 24 months of follow-up, the best program retained 85% of patients and the worst retained 46%. Attrition was higher in studies with shorter reporting periods, leading to monthly weighted mean attrition rates of 3.3%/month, 1.9%/month, and 1.6%/month for studies reporting to 6, 12, and 24 months, respectively, and suggesting that overall patient retention may be overestimated in the published reports. In sensitivity analyses, estimated retention rates ranged from 24% in the worse case to 77% in the best case at the end of 2 years, with a plausible midpoint scenario of 50%. Since the inception of large-scale antiretroviral therapy access early in this decade, antiretroviral therapy programs in Africa have retained about 60% of their patients at the end of 2 years. Loss to follow-up was the major cause of attrition, followed by death. Better patient tracing procedures, better understanding of loss to follow-up, and earlier initiation of antiretroviral therapy to reduce mortality are needed if retention is to be improved. Retention varies widely across programmes, and programmes that have achieved higher retention rates can serve as models for future improvements. **Editors' note: An estimated half of people starting antiretroviral treatment in Africa in programmes that publish their results are no longer receiving treatment after two years. Starting treatment earlier to prevent mortality and concerted efforts to discover and remedy the conditions that lead people to drop out of programmes are obvious first steps. Sharing what works in patient monitoring and tracing, as well as in overcoming transport, nutritional, financial, and other barriers, is urgently needed.**

Toure S, Kouadio B, Seyler C, Traore M, Dakoury-Dogbo N, Duvignac J, Diakite N, Karcher S, Grundmann C, Marlink R, Dabis F, Anglaret X; Aconda Study Group. Rapid scaling-up of antiretroviral therapy in 10,000 adults in Côte d'Ivoire: 2-year outcomes and determinants. *AIDS.* 2008;22(7):873-82.

Toure and colleagues aimed to assess the rates and determinants of mortality, loss to follow-up, and immunological failure in a nongovernmental organization-implemented program of access to antiretroviral treatment in Côte d'Ivoire. In each new treatment center, professionals were trained in HIV care, and a computerized data system was implemented. Individual patient and programme level determinants of survival, loss to follow-up and immunological failure were assessed by multivariate analysis. Between May 2004 and February 2007, 10,211 patients started antiretroviral treatment in 19 clinics (median pre-antiretroviral treatment CD4 cell count, 123 cells/microl; initial regimen zidovudine-lamivudine-efavirenz, 20%; stavudine-lamivudine-efavirenz, 22%; stavudine-lamivudine-nevirapine, 52%). At 18 months on antiretroviral treatment, the median gain in CD4 cell count was +202 cells/microlitre, the probability of death was 0.15, and the probability of being loss to follow-up was 0.21. In addition to the commonly reported determinants of impaired outcomes (low CD4 cell count, low BMI, low haemoglobin, advanced clinical stage, old age and poor adherence), two factors were also shown to independently jeopardize prognosis: male sex (men vs. women: hazard ratio = 1.52 for death, 1.27 for loss to follow-up, 1.31 for immunological failure); and attending a recently opened clinic (inexperienced vs. experienced centers: hazard ratio = 1.40 for death, 1.58 for loss to follow-up). None of the three outcomes was associated with the drug regimen. In this rapidly scaling-up program, survival and immune reconstitution were good; women and patients followed up in centers with longer experience had better outcomes; and outcomes were similar in zidovudine/stavudine-based regimens and in efavirenz/nevirapine-based regimens. Decreasing the rate of loss to follow-up should now be the top priority in antiretroviral treatment rollout. **Editors' note: An easy-to-manage computerized data monitoring system in 10 mostly primary health care units provided real-time indicators of numbers of patients in care and their treatment progress. Male sex was associated with immunological failure, mortality, and higher rates of programme withdrawal, suggesting that these are interlinked. Experienced centres should be twinned with new treatment centres for assistance in monitoring and improving the economical, managerial, logistical, and organizational characteristics that influence patient outcomes.**

8. *Male circumcision*

Weiss HA, Plummer ML, Changalucha J, Mshana G, Shigongo ZS, Todd J, Wight D, Hayes RJ, Ross DA. Circumcision among adolescent boys in rural northwestern Tanzania. *Trop Med Int Health*. 2008 Jun 18. [Epub ahead of print]

Male circumcision reduces risk of HIV among heterosexual men by about 60%. Modelling the impact of circumcision on HIV transmission, and planning service expansion, relies on self-reported circumcision status. Weiss and colleagues investigated the validity of self-reported status. Survey and in-depth interview data from adolescents enrolled in a community randomized sexual health intervention trial in rural Mwanza, Tanzania were analysed. The 5354 male school attenders (median age 15.5 years) were recruited in 1998 and followed for 3 years. At baseline, circumcision prevalence was 13.7% by self-report and 11.8% by clinical examination, rising to 17.3% by clinical examination at final survey. Only 61.5% of Muslim males were circumcised at the final survey. Of 506 participants who reported being circumcised at baseline, only 78.9% reported this at interim. Similarly, only 84.2% of participants clinically assessed as circumcised at baseline were also assessed as circumcised at interim. At both baseline and interim surveys, about 80% of participants who reported being circumcised were also found to be so at clinical examination. There was a high

tolerance and respect for circumcision among male in-depth interview respondents, with widespread belief that it was beneficial for penile hygiene and disease prevention. The majority of female in-depth interview respondents said that they did not know what male circumcision was. Attitudes to male circumcision were positive in this population despite its low prevalence. There were substantial inconsistencies in both self-reported and clinically assessed circumcision status. Methods are needed to improve self-report and training of clinicians in this setting. **Editors' note: It is important to note that the association between self-reported circumcision status and HIV infection will be underestimated in demographic and health surveys if misclassification is independent of HIV status. Both natural foreskin length variation and partial circumcision techniques (e.g. removing only the tip of the foreskin) may explain some self-report misclassification. Since residual foreskin likely reduces the protective effect of male circumcision, should we start classifying circumcision status by length of foreskin rather than by yes/no categories?**

9. Morbidity and co-morbidity

Harris M. Nephrotoxicity associated with antiretroviral therapy in HIV-infected patients. *Expert Opin Drug Saf.* 2008;7(4):389-400.

With the success of modern antiretroviral therapies in increasing longevity of patients with HIV infection, chronic conditions including renal disease have assumed a greater importance in patient management. Some antiretroviral therapies have themselves been identified to have clinically significant nephrotoxicity. Harris and colleagues aimed to review the risk factors and mechanisms for renal toxicity of antiretroviral drugs, and their impact on the clinical management of patients with HIV. Current literature and HIV treatment guidelines were reviewed. Background rates of renal disease and associated risk factors were significant in the HIV clinic population, and renal function should be assessed in all HIV-infected patients. Modern HIV treatment regimens have a relatively low but clinically significant nephrotoxic potential; therefore, renal function should be evaluated on an ongoing basis in patients receiving antiretroviral therapy. **Editors' note: HIV can have direct effects on the kidney (HIV-associated nephropathy or HIVAN and thrombotic micro-blood vessel disease) and the body's immune response can cause glomerulonephritis (local inflammation). HIVAN responds to antiretroviral therapy suppressing HIV but some antiretroviral drugs can have direct toxic effects on the kidney or can cause renal dysfunction indirectly. People living with HIV can also have other conditions affecting kidney function (hepatitis B or C, other liver disease, syphilis, diabetes, hypertension, recreational drug use, family history) and HIV-related renal disease tends to increase as CD4 count falls and viral load rises, therefore it is important to monitor kidney function regularly.**

Sheth PM, Sunderji S, Shin LY, Rebbapragada A, Huibner S, Kimani J, Macdonald KS, Ngugi E, Bwayo JJ, Moses S, Kovacs C, Loutfy M, Kaul R. Coinfection with Herpes Simplex Virus Type 2 Is Associated with Reduced HIV-Specific T Cell Responses and Systemic Immune Activation. *J Infect Dis.* 2008;197(10):1394-1401.

Chronic coinfection with herpes simplex virus type 2 (HSV-2) and human immunodeficiency virus (HIV) has been associated with an increased HIV viral load and more rapid disease progression, perhaps related to HSV-2-associated alterations in host immunity. Studies were nested within (1) a cross-sectional study of men coinfecting with HIV and HSV-2 and (2) women not infected with HIV, both before and after HSV-2 acquisition. HSV-2 infection

status was determined by ELISA. HIV-specific CD8(+) T cell epitopes were mapped, and proliferation of HIV-specific cells was also assessed. Systemic inflammatory and regulatory T cell populations were assayed by flow cytometry. The breadth of both the HIV-specific CD8(+) T cell interferon-gamma and proliferative responses was reduced in participants coinfected with HIV and HSV-2, independent of the HIV plasma viral load and CD4(+) T cell count, and the magnitude of the responses was also reduced. HSV-2 infection in this group was associated with increased T cell CD38 expression but not with differences in the proportion of CD4(+) FoxP3(+) regulatory T cells. However, in women not infected with HIV, acquisition of HSV-2 was associated with an increase in the proportion of regulatory T cells. In conclusion, HSV-2 coinfection was associated with reduced HIV-specific T cell responses and systemic inflammation. The immune effects of HSV-2 may underlie the negative impact that this coinfection has on the clinical course of HIV infection. **Editors' note: Up to 80% of people living with HIV infection in sub-Saharan Africa have herpes simplex virus-2 (HSV-2) co-infection which appears to be associated with reduced HIV-specific T cell responses. Co-infection may be associated with a higher viral load, systemic inflammation due to activation of host Toll-like receptors, and HIV progression. Confirmation of research findings suggesting that HSV-2 treatment may delay HIV disease progression is urgently needed.**

10. Resilience

Murphy DA, Marelich WD. Resiliency in young children whose mothers are living with HIV/AIDS. *AIDS Care*. 2008;20(3):284-91.

Resiliency was investigated among well children 6-11 years of age (N = 111) whose mothers were living with AIDS or were HIV symptomatic to determine if mother's HIV status was a risk factor that could effect child resiliency, as well as to investigate other factors associated with resiliency. Assessments were conducted with mother and child dyads over four time points (baseline, 6-, 12-, and 18-month follow-ups). Maternal illness was a risk factor for resiliency: as maternal viral load increased, resiliency was found to decrease. Longitudinally, resilient children had lower levels of depressive symptoms (by both mother and child report). Resilient children also reported higher levels of satisfaction with coping self-efficacy. A majority of the children were classified as non-resilient; implications for improving resiliency among children of HIV-positive mothers are discussed. **Editors' note: Resiliency at the individual level, as opposed to community resilience, refers to a person's capacity for successful adaptation despite challenging circumstances. Rather than simply avoiding negative outcomes, resilience means demonstrating adequate adaptation in the presence of adversity. Resilient children have a more active approach to problem solving, tend to perceive experiences constructively, have better self-esteem, and have high self-reports of effectiveness. A strong adult attachment, problem solving and coping skills training, and psychotherapeutic interventions for depression can help build resiliency in vulnerable children.**

11. National responses - strategic planning

Walensky RP, Wood R, Weinstein MC, Martinson NA, Losina E, Fofana MO, Goldie SJ, Divi N, Yazdanpanah Y, Wang B, Paltiel AD, Freedberg KA; CEPAC International Investigators. Scaling Up Antiretroviral Therapy in South Africa: The Impact of Speed on Survival. *J Infect Dis*. 2008 May 1;197(9):1324-1332.

Only 33% of eligible human immunodeficiency virus (HIV)-infected patients in South Africa receive antiretroviral therapy. Walensky and co-authors sought to estimate the impact of alternative antiretroviral therapy scale-up scenarios on patient outcomes from 2007-2012. Using a simulation model of HIV infection with South African data, they projected HIV-associated mortality with and without effective antiretroviral therapy for an adult cohort in need of therapy (2007) and for adults who became eligible for treatment (2008-2012). The authors compared 5 scale-up scenarios: (1) zero growth, with a total of 100,000 new treatment slots; (2) constant growth, with 600,000; (3) moderate growth, with 2.1 million; (4) rapid growth, with 2.4 million; and (5) full capacity, with 3.2 million. The projections showed that by 2011, the rapid growth scenario fully met the South African need for antiretroviral therapy; by 2012, the moderate scenario met 97% of the need, but the zero and constant growth scenarios met only 28% and 52% of the need, respectively. The latter scenarios resulted in 364,000 and 831,000 people alive and on antiretroviral therapy in 2012. From 2007 to 2012, cumulative deaths in South Africa ranged from 2.5 million under the zero growth scenario to 1.2 million under the rapid growth scenario. Alternative antiretroviral therapy scale-up scenarios in South Africa will lead to differences in the death rate that amount to more than 1.2 million deaths by 2012. More rapid scale-up remains critically important. **Editors' note: Decision-makers can be influenced by modelling which demonstrates the differential impact of choosing various scale-up strategies for programmes. In this case, the speed of treatment scale-up has a large effect on the number of citizens alive in 2012. Although South Africa now has the highest number of people on antiretroviral treatment, two-thirds of eligible people are awaiting the expedient scale-up of services that will make a striking difference to their lives.**

12. Treatment and care

Grabar S, Lanoy E, Allavena C, Mary-Krause M, Bentata M, Fischer P, Mahamat A, Rabaud C, Costagliola D; on behalf of the Clinical Epidemiology Group of the French Hospital Database on HIV. Causes of the first AIDS-defining illness and subsequent survival before and after the advent of combined antiretroviral therapy. *HIV Med.* 2008;(4):246-256.

Grabar and colleagues aimed to analyse the impact of combined antiretroviral treatment on survival with AIDS, according to the nature of the first AIDS-defining clinical illness; and to examine trends in AIDS-defining causes and non-AIDS-defining causes of death. From the French Hospital Database on HIV, they studied trends in the nature of the first AIDS-defining clinical illness and subsequent survival in France during three calendar periods: the pre-combined antiretroviral treatment period (1993-1995; 8027 patients), the early combined antiretroviral treatment period (1998-2000; 3504 patients) and the late combined antiretroviral treatment period (2001-2003; 2936 patients). In the pre-combined antiretroviral treatment period the three most frequent initial AIDS-defining clinical illnesses were Pneumocystis carinii (jirovecii) pneumonia (15.6%), oesophageal candidiasis (14.3%) and Kaposi's sarcoma (13.9%). In the late combined antiretroviral treatment period, the most frequent AIDS-defining clinical illness were tuberculosis (22.7%), Pneumocystis carinii (jirovecii) pneumonia (19.1%) and oesophageal candidiasis (16.2%). The risk of death after a first AIDS-defining clinical illness fell significantly after the arrival of combined antiretroviral treatment. Lower declines were observed for progressive multifocal leukoencephalopathy, lymphoma, and Mycobacterium avium complex infection. After an AIDS-defining clinical illness, the 3-year risk of death from an AIDS-defining cause fell fivefold between the pre-combined antiretroviral treatment and late combined antiretroviral

treatment periods (39%vs. 8%), and fell twofold for non-AIDS-defining causes (17%vs. 9%). The authors conclude that the relative frequencies of initial AIDS-defining clinical illness have changed since the advent of combined antiretroviral treatment. Tuberculosis is now the most frequent initial AIDS-defining clinical illness in France; this is probably the result of the increasing proportion of migrants from sub-Saharan Africa. After a first AIDS-defining clinical illness, combined antiretroviral treatment has a major impact on AIDS-defining causes and a smaller impact on deaths from other causes. The risk of death from AIDS and from other causes is now similar. **Editors' note: Monitoring the evolution in initial AIDS-defining illnesses with the introduction of antiretroviral treatment and changing patient demographics, such as been done in France, is useful for adapting services to new disease and patient profiles. The dramatic reductions in mortality in France reflect the transformation of AIDS into a chronic, manageable disease for the majority of patients in this high-income country.**

Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, Loutfy MR, Lennox JL, Gatell JM, Rockstroh JK, Katlama C, Yeni P, Lazzarin A, Clotet B, Zhao J, Chen J, Ryan DM, Rhodes RR, Killar JA, Gilde LR, Strohmaier KM, Meibohm AR, Miller MD, Hazuda DJ, Nessel ML, DiNubile MJ, Isaacs RD, Nguyen BY, Tepler H; BENCHMRK Study Teams. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med*. 2008;359(4):339-54.

Raltegravir (MK-0518) is an inhibitor of human immunodeficiency virus type 1 (HIV-1) integrase active against HIV-1 susceptible or resistant to older antiretroviral drugs. Steigbigel and colleagues conducted two identical trials in different geographic regions to evaluate the safety and efficacy of raltegravir, as compared with placebo, in combination with optimized background therapy, in patients infected with HIV-1 that had triple-class drug resistance in whom antiretroviral therapy had failed. Patients were randomly assigned to raltegravir or placebo in a 2:1 ratio. In the combined studies, 699 of 703 randomized patients (462 and 237 in the raltegravir and placebo groups, respectively) received the study drug. Seventeen of the 699 patients (2.4%) discontinued the study before week 16. Discontinuation was related to the study treatment in 13 of these 17 patients: 7 of the 462 raltegravir recipients (1.5%) and 6 of the 237 placebo recipients (2.5%). The results of the two studies were consistent. At week 16, counting non-completion as treatment failure, 355 of 458 raltegravir recipients (77.5%) had HIV-1 RNA levels below 400 copies per millilitre, as compared with 99 of 236 placebo recipients (41.9%, $P < 0.001$). Suppression of HIV-1 RNA to a level below 50 copies per millilitre was achieved at week 16 in 61.8% of the raltegravir recipients, as compared with 34.7% of placebo recipients, and at week 48 in 62.1% as compared with 32.9% ($P < 0.001$ for both comparisons). Without adjustment for the length of follow-up, cancers were detected in 3.5% of raltegravir recipients and in 1.7% of placebo recipients. The overall frequencies of drug-related adverse events were similar in the raltegravir and placebo groups. The authors conclude that in HIV-infected patients with limited treatment options, raltegravir plus optimized background therapy provided better viral suppression than optimized background therapy alone for at least 48 weeks. (ClinicalTrials.gov numbers, NCT00293267 and NCT00293254.) **Editors' note: Integrase is a viral enzyme that catalyzes the insertion of proviral DNA into the host-cell genome. Even when HIV strains are resistant to other classes of antiretroviral drugs, the distinct mechanism of action of integrase inhibitors, in combination with optimized**

background therapy, can reduce viral load and increase CD4 counts, as shown in this study of patients with triple-class drug resistance.

13. Structural determinants

Pearce ME, Christian WM, Patterson K, Norris K, Moniruzzaman A, Craib KJ, Schechter MT, Spittal PM. The Cedar Project: Historical trauma, sexual abuse and HIV risk among young Aboriginal people who use injection and non-injection drugs in two Canadian cities. *Soc Sci Med*. 2008;66(11):2185-2194.

Recent Indigenist scholarship has situated high rates of traumatic life experiences, including sexual abuse, among Indigenous peoples of North America within the larger context of their status as colonized peoples. Sexual abuse has been linked to many negative health outcomes including mental, sexual and drug-related vulnerabilities. There is a paucity of research in Canada addressing the relationship between antecedent sexual abuse and negative health outcomes among Aboriginal people including elevated risk of HIV infection. The primary objectives of this study were to determine factors associated with sexual abuse among participants of the Cedar Project, a cohort of young Aboriginal people between the ages of 14 and 30 years who use injection and non-injection drugs in two urban centres in British Columbia, Canada; and to locate findings through a lens of historical and intergenerational trauma. Pearce and colleagues utilized post-colonial perspectives in research design, problem formulation and the interpretation of results. Multivariate modelling was used to determine the extent to which a history of sexual abuse was predictive of negative health outcomes and vulnerability to HIV infection. Of the 543 eligible participants, 48% reported ever having experienced sexual abuse; 69% of sexually abused participants were female. The median age of first sexual abuse was 6 years for both female and male participants. After adjusting for socio-demographic variables and factors of historical trauma, sexually abused participants were more likely to have ever been on the streets for more than three nights, to have ever self-harmed, to have suicide ideation, to have attempted suicide, to have a diagnosis of mental illness, to have been in the emergency department within the previous 6 months, to have had over 20 lifetime sexual partners, to have ever been paid for sex, and to have ever overdosed. The prevalence and consequences of sexual abuse among Cedar Project participants are of grave concern. Sexual trauma will continue to affect individuals, families, and communities until unresolved historical trauma is meaningfully addressed in client-driven, culturally safe programming. **Editors' note: Sexual abuse within Aboriginal communities in Canada is believed to have been relatively rare prior to European contact and the residential school system. In 2005, Aboriginal people comprised 3.3% of the Canadian population, 7.5% of HIV infections, and 22% of new infections. The link between sexual abuse and vulnerability to negative sexual and mental health disorders, including HIV infection, has been documented around the world. In Canada and elsewhere, stopping sexual abuse requires zero tolerance community norms that are rooted in a clear understanding of its origins in historical trauma at individual, family, and community levels.**

That was *HIV this week*, signing off.

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