

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

Welcome to the 58<sup>th</sup> issue of *HIV This Week*! In this issue, we cover **surgery** (time for Iranian surgeons to double glove; what does surgery have to do with the Millennium Development Goals?), **sexual transmission** (rethinking the probability of heterosexual transmission; the rationale for herpes suppression to reduce genital HIV shedding), **rectal microbicides** (promising news from the first rectal-challenge macaque study), **concurrency** (from Tanzania: why it is important to ask both women and men about sexual behaviour; from Nigeria: the need for a better definition of concurrency), **drug resistance** (17% of antiretroviral-naïve patients have minority resistant variants), **economics** (the rationale for free antiretroviral treatment at point of care; why and how to monitor effectiveness, efficiency, equity, and acceptability of programmes or services), **paediatrics** (high time to treat kids with effective drug formulations; cognitive deficits in infected and affected kids in Kinshasa), **men who have sex with men** (challenging 'heteronormativity' and ending exclusion), **structural determinants and approaches** (changing the playing field to change the play), **prevention** (doing better, stronger, faster), **treatment** (from Cambodia: switching to full dose nevirapine without dose escalation), and **epidemiology** (the inner workings of the updated Spectrum; tracking HIV's travels from Yunnan, China through molecular epidemiology; time for intensified harm reduction: Bangladesh moves from a low level to a concentrated epidemic).

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### 1. *Surgery*

Moghimi M, Marashi SA, Kabir A, Taghipour HR, Faghihi-Kashani AH, Ghoddoosi I, Alavian SM. Knowledge, attitude, and practice of Iranian surgeons about blood-borne diseases. *J Surg Res*. 2008 Feb 1. [Epub ahead of print]

Perhaps more than any other healthcare worker, it is the surgeons who are at an increased risk of exposure to hepatitis B (HB) virus, hepatitis C virus, and human immunodeficiency

virus. The aim of this study was to evaluate surgeons' concerns regarding risk awareness and behavioral methods of protection against blood-borne pathogen transmission during surgery. A 31-item questionnaire with a reliability coefficient of 0.73 was used. Of 575 surgeons invited to participate from three universities and one national annual surgical society between May and July 2007, 430 (75%) returned completed forms. Concern about being infected with blood-borne diseases was more than 70 (from a total score of 100). Only 12.9% of surgeons always used double gloves. Complete vaccination against HB was done in about 76% of surgeons and only 56.8% had checked their HB surface antibody (anti-HBs) level. Older surgeons never used double gloves ( $P = 0.001$ ). Iranian surgeons are not aware of the correct percentage of infected patients with and seroconversion rate of blood-borne diseases, do not use double gloves adequately, do not report their needlestick injuries, vaccinate against HB, and check anti-HBs after vaccination. Educational meetings, pamphlets, and facilities must be provided to health care workers, informing them of hazards, prevention, and postexposure prophylaxis to needlestick injuries, vaccination efficacy, and wearing double gloves. **Editors' note: These middle-aged surgeons with relatively high surgical experience have not translated their concerns about the risk of blood-borne transmission into highly effective protection strategies. Double gloving, which increases protection by providing a second barrier, is more common among younger surgeons who need to encourage this practice as a surgical norm among their elders, along with masks and protective glasses.**

PLoS Medicine Editors. PLoS Med. 2008 Aug 26;5(8):e182. A crucial role for surgery in reaching the UN Millennium Development Goals.

Recent efforts to bring surgery into the global health conversation have focused on arguments that surgical conditions should be considered as "neglected diseases" that disproportionately affect the world's poorest people. There are at least five important reasons why providing surgery services should be considered a global public health priority. First, surgical conditions constitute a substantial global burden of disease, led by injuries, followed by malignancies, congenital anomalies, pregnancy complications, cataracts, and perinatal conditions. Second, surgery is a global public health issue because of global disparities in surgical care: 30% of the world's population receives 73.6% of the estimated 234.2 million major surgical procedures performed worldwide each year, with the poorest third receiving only 3.5%. Third, surgery can be remarkably cost-effective when compared with some of the interventions that are considered the building blocks of global public health. Fourth, building surgical services, which requires infrastructure, supplies, and human resources, may in turn help to build health systems and to strengthen primary care. Finally, it is feasible to deliver surgical services even in the most resource-constrained settings. Surgery could play an essential role in meeting many of the 2015 United Nations Millennium Development Goals. For example, trauma care, obstetric surgery, and general surgical services are essential components in reaching goal 4 (reducing child mortality) and goal 5 (improving maternal health). Surgery can play a role in tackling infectious diseases (goal 6): male circumcision may reduce the risk of men acquiring HIV through heterosexual sex by 60%. With foresight and planning, the impending scale-up of male circumcision services in Africa could help to provide the infrastructure to build surgical services more generally. The authors argue that there is even a link between surgery and goal 1, the goal of halving the number of people living in poverty. A survey of patients at the Aravind Eye Hospital in Madurai, India found that 85% of men and 58% of women who had lost their jobs as a result

of blindness from cataract regained those jobs after surgery. "Improving surgical capacity at district hospital level" was among the top 30 solutions at this year's Copenhagen Consensus meeting of distinguished economists to the question of how best to advance global welfare, especially the welfare of the developing world. The authors conclude that surgery is beginning to outgrow its status as the "neglected stepchild of global public health". **Editors' notes: If this open-access article sensitises surgeons around the world to the potential that their skills can play in achieving human development goals and if the skills of those who are motivated, culturally sensitive, and willing to learn from their national counterparts can be channelled by locally led teams into effective and high quality surgical services for the underserved, then surgery will no longer be a 'neglected disease'.**

## **2. Sexual Transmission**

Powers KA, Poole C, Pettifor AR, Cohen MS. Rethinking the heterosexual infectivity of HIV-1: a systematic review and meta-analysis. *Lancet* 2008 Published online August 5, 2008 DOI:10.1016/S1473-3099(08)70156-7

Studies of cumulative HIV incidence suggest that cofactors such as genital ulcer disease, HIV disease stage, and male circumcision influence HIV transmission; however, the heterosexual infectivity of HIV-1 is commonly cited as a fixed value (approximately 0.001, or one transmission per 1000 contacts). Powers et al sought to estimate transmission cofactor effects on the heterosexual infectivity of HIV-1 and to quantify the extent to which study methods have affected infectivity estimates. They undertook a systematic search (up to April 27, 2008) of PubMed, Web of Science, and relevant bibliographies to identify articles estimating the heterosexual infectivity of HIV-1. They used meta-regression and stratified random-effects meta-analysis to assess differences in infectivity associated with cofactors and study methods. Infectivity estimates were very heterogeneous, ranging from zero transmissions after more than 100 penile-vaginal contacts in some serodiscordant couples to one transmission for every 3.1 episodes of heterosexual anal intercourse. Estimates were only weakly associated with study methods. Infectivity differences, expressed as number of transmissions per 1000 contacts, were 8.1 (95 % CI 0.4-15.8) when comparing uncircumcised to circumcised susceptible men, 6.0 (3.3-8.8) comparing susceptible individuals with and without genital ulcer disease, 1.9 (0.9-2.8) comparing late-stage to midstage index cases, and 2.5 (0.2-4.9) comparing early-stage to mid-stage index cases. A single value for the heterosexual infectivity of HIV-1 fails to reflect the variation associated with important cofactors. The commonly cited value of 0.001 was estimated among stable couples with low prevalences of high-risk cofactors, and represents a lower bound. Cofactor effects are important to include in epidemic models, policy considerations, and prevention messages. **Editors' note: The findings of this systematic analysis suggest that in many contexts, such as lack of male circumcision, presence of sexually transmitted infections, practice of anal sex, and early-stage or late-stage infection, heterosexual infectivity of HIV-1 might exceed the commonly cited value of one-in-a-thousand by more than an order of magnitude (i.e. more than one-in-a-hundred). Other cofactors, for which there are insufficient data but that clearly may play a role, such as viral load, viral subtype, and antiretroviral drug use, can further increase or decrease transmission probabilities. Since the overall probability of HIV transmission also depends on the probability of exposure to HIV in the first place, we need to work on the determinants of exposure as well as the co-factors for transmission.**

Nagot N, Ouedraogo A, Konate I, Weiss HA, Foulongne V, Defer MC, Sanon A, Becquart P, Segondy M, Sawadogo A, Van de Perre P, Mayaud P; ANRS 1285 Study Group. Collaborators (26) Bahemba E, Berthe A, Coulibaly M, Defer MC, Diallo R, Djagbare D, Konate I, Ky-Dama F, M'Boutiki GT, Meda N, Millogo I, Ouedraogo A, Ouedraogo D, Rouet F, Sanon A, Sawadogo H, Vallo R, Andonaba JB, Sawadogo A, Mayaud P, Weiss HA, Nagot N, Becquart P, Foulongne V, Segondy M, Van de Perre P. Roles of clinical and subclinical reactivated herpes simplex virus type 2 infection and human immunodeficiency virus type 1 (HIV-1)-induced immunosuppression on genital and plasma HIV-1 levels. *J Infect Dis.* 2008 Jul 15;198(2):241-9.

Few longitudinal studies have described the interactions between reactivation of herpes simplex virus type 2 (HSV-2) infection (hereafter, "HSV-2 reactivation") and genital and systemic replication of human immunodeficiency virus type 1 (HIV-1). Women in Burkina Faso who were seropositive for both HIV-1 and HSV-2 were enrolled in a randomized placebo-controlled trial of therapy to suppress reactivation of HSV-2 infection (hereafter, "HSV suppressive therapy"). During the baseline phase, 6 enriched cervicovaginal lavage specimens were obtained over 12 weeks to detect and quantify the HIV-1 RNA and HSV-2 DNA loads. Women with genital ulcer disease (GUD) detected at least once were more likely than women in whom GUD was not detected (risk ratio [RR], 1.23; 95% confidence interval [CI], 1.09-1.37) to have genital HIV-1 RNA detected during  $\geq 1$  visit. Similarly, women with genital HSV-2 DNA detected during  $\geq 1$  clinic visit were more likely than women in whom genital HSV-2 DNA was not detected (RR, 1.17; 95% CI, 1.01-1.34) to have genital HIV-1 RNA detected at least once. In addition, the mean genital HIV-1 RNA loads for women with GUD detected during  $\geq 1$  visit and women with HSV-2 genital shedding detected during  $\geq 1$  visit were greater than that for women in whom genital HSV-2 DNA or GUD was never detected. The plasma HIV-1 RNA load was increased among women for whom  $\geq 1$  visit revealed GUD (+0.25 log(10) copies/mL; 95% CI, -0.05-0.55) or genital HSV-2 DNA (+0.40 log(10) copies/mL; 95% CI, 0.15-0.66), compared with women who did not experience GUD or HSV-2 genital shedding, respectively. The association of HSV-2 reactivations on HIV-1 replication tended to be stronger in patients with a higher CD4(+) cell count (i.e.,  $>500$  cells/microl). The contribution of HSV-2 to HIV-1 replication among women with CD4(+) cell count of  $\leq 500$  cells/microl was reduced because almost all experienced HIV-1 genital shedding. Both clinical and subclinical HSV-2 reactivations play a role in increasing the rate of HIV-1 replication. HSV suppressive therapy is a promising tool for HIV control. Initiation of such therapy when the CD4(+) cell count is  $>500$  cells/microl deserves further investigation. **Editors' note: More than 70% of people living with HIV in high-income, middle-income, and low-income countries may be co-infected with herpes simplex virus type 2 (HSV-2). This study of 136 women who were moderately immunosuppressed but not on antiretroviral treatment and who contributed data from 784 study visits, demonstrates that both clinical (i.e. symptomatic with genital ulcers) and subclinical (i.e. no symptoms) HSV-2 reactivations contribute to HIV replication in the plasma and to genital HIV shedding. Because HSV-2 suppressive therapy has the potential to both prevent onward transmission and slow HIV disease progression, consideration may be given to offering it to people with known HIV-positive status who present with genital ulcer disease, to take until they become eligible for antiretroviral treatment, pending further studies.**

### 3. *Rectal microbicides*

Cranage M 1, Sharpe S 2, Herrera C 1, Cope A 1, Dennis M 2, Berry N 3, Ham C, Heeney J 4,5, Rezk N 6, Kashuba A 6, Anton P 7, McGowan I 7x, Shattock R 1. Prevention of SIV rectal transmission and priming of T cell responses in macaques after local pre-exposure application of tenofovir gel. PLoS Med August 2008 | Volume 5 | Issue 8 | e157

The rectum is particularly vulnerable to HIV transmission having only a single protective layer of columnar epithelium overlying tissue rich in activated lymphoid cells; thus, unprotected anal intercourse in both women and men carries a higher risk of infection than other sexual routes. In the absence of effective prophylactic vaccines, increasing attention is being given to the use of microbicides and preventative antiretroviral (ARV) drugs. To prevent mucosal transmission of HIV, a microbicide/ARV should ideally act locally at and near the virus portal of entry. As part of an integrated rectal microbicide development programme, we have evaluated rectal application of the nucleotide reverse transcriptase (RT) inhibitor tenofovir (PMPA, 9-[(R)-2-(phosphonomethoxy) propyl] adenine monohydrate), a drug licensed for therapeutic use, for protective efficacy against rectal challenge with simian immunodeficiency virus (SIV) in a well-established and standardised macaque model. In this study a total of 20 purpose-bred Indian rhesus macaques were used to evaluate the protective efficacy of topical tenofovir. Nine animals received 1% tenofovir gel per rectum up to 2 h prior to virus challenge, four macaques received placebo gel, and four macaques remained untreated. In addition, three macaques were given tenofovir gel 2 h after virus challenge. Following intrarectal instillation of 20 median rectal infectious doses (MID50) of a noncloned, virulent stock of SIVmac251/32H, all animals were analysed for virus infection, by virus isolation from peripheral blood mononuclear cells (PBMC), quantitative proviral DNA load in PBMC, plasma viral RNA (vRNA) load by sensitive quantitative competitive (qc) RT-PCR, and presence of SIV-specific serum antibodies by ELISA. Cranage et al report here a significant protective effect ( $p= 0.003$ ; Fisher exact probability test) wherein eight of nine macaques given tenofovir per rectum up to 2 h prior to virus challenge were protected from infection ( $n=6$ ) or had modified virus outcomes ( $n=2$ ), while all untreated macaques and three of four macaques given placebo gel were infected, as were two of three animals receiving tenofovir gel after challenge. Moreover, analysis of lymphoid tissues post mortem failed to reveal sequestration of SIV in the protected animals. They found a strong positive association between the concentration of tenofovir in the plasma 15 min after rectal application of gel and the degree of protection in the six animals challenged with virus at this time point. Moreover, colorectal explants from non-SIV challenged tenofovir-treated macaques were resistant to infection *ex vivo*, whereas no inhibition was seen in explants from the small intestine. Tissue-specific inhibition of infection was associated with the intracellular detection of tenofovir. Intriguingly, in the absence of seroconversion, Gag-specific gamma interferon (IFN- $\gamma$ )- secreting T cells were detected in the blood of four of seven protected animals tested, with frequencies ranging from 144 spot forming cells (SFC)/10<sup>6</sup> PBMC to 261 spot forming cells (SFC)/10<sup>6</sup> PBMC. These results indicate that colorectal pre-treatment with ARV drugs, such as tenofovir, has potential as a clinically relevant strategy for the prevention of HIV transmission. Cranage et al conclude that plasma tenofovir concentration measured 15 min after rectal administration may serve as a surrogate indicator of protective efficacy. This may prove to be useful in the design of clinical studies. Furthermore, *in vitro* intestinal explants served as a model for drug distribution *in vivo* and susceptibility to virus infection. The finding of T cell priming following exposure to virus in the absence of overt infection is provocative. Further studies

would reveal if a combined modality microbicide and vaccination strategy is feasible by determining the full extent of local immune responses induced and their protective potential. **Editors' note: This preclinical study using the simian immunodeficiency virus (SIV)-macaque model is a promising start in the race to develop an effective rectal microbicide. The strong association seen between plasma tenofovir levels 15 minutes after rectal gel application and the degree of protection, as well as the interesting finding of primed SIV-specific T cells in some of the protected animals, need to be confirmed in further pre-clinical studies.**

#### **4. Concurrency**

Vissers DCJ, Voeten HACM, Urassa M, Isingo R, Ndege M, Kumogola Y, Mwaluko G, Zaba B, De Vlas SJ and Habbema JDF. Separation of spouses due to travel and living apart raises HIV risk in Tanzanian couples. *Sexually Transmitted Diseases*, August 2008, Vol. 35, No. 8, p.714-720

Persons with absent partners may be more vulnerable to risky sexual behaviour and therefore HIV. Partner absence can be due to travelling (e.g. family visits or funerals) or to living apart (e.g. work-related or in polygamous marriages). Debby et al investigated to what extent partner absence leads to more risky sexual behaviour in Tanzanian couples. They compared 95 men and 85 women living apart with 283 men and 331 women living together. Only persons who were still married were included, either living apart or cohabiting at the time of the interview. Subjects were classified into 4 groups: coresidents being either nonmobile or mobile, and people living apart either frequently or infrequently seeing each other. Most people living apart were polygamously married. Men living apart did not report more extramarital sex than coresident men. However, among coresident men, extramarital sex was reported by 35% of those being mobile compared with 15% of those nonmobile. Among women, those living apart reported extramarital sex more often than coresidents (14% vs. 7%), and this was mainly due to women living apart who infrequently saw their husbands. Risky sexual behaviour occurs more often in mobile coresident men, and in women living apart infrequently seeing their spouses. These groups are relatively easy to identify and need extra attention in HIV prevention campaigns. **Editors' note: Concurrent relationships, multiple partners, and mobility are known to be associated with an increased risk of HIV exposure. The results of this study of couples, who were co-resident in 1996 and still married in 2002 according to both partners, emphasise the importance of studying the sexual behaviour of both sexes. Although most couples living apart in this area of north-western Tanzania were in polygamous marriages, living apart was not associated with increased extramarital sex in men but it was in women. Being mobile was a risk factor for unprotected extramarital sex in men but not in women. Promoting condom use for extramarital encounters is an obvious first step but a better understanding of the determinants of sexual risk behaviour in women living apart is needed to inform effective prevention programmes.**

Uthman OA, Kongnyuy EJ. A multilevel analysis of effect of neighbourhood and individual wealth status on sexual behaviour among women: evidence from Nigeria 2003 Demographic and Health Survey. *BMC Int Health Hum Rights*. 2008 Jun 27;8:9

Nigeria is home to more people living with HIV than any other country in the world, except South Africa and India - where an estimated 2.9 million [1.7 million - 4.2 million] people were living with the virus in 2005. Women bear the greatest burden of frequent high-risk pregnancies, raising large families, and increasingly, the AIDS epidemic. Thus, there is a

need for better understanding of the determinants of high risk sexual behaviour among women. In this study, Uthman et al examined factors associated with extra-marital sex among women in Nigeria and investigated how much variation in reported extra-marital sex can be attributed to individual-, and community-level factors. Uthman et al analyzed data from 6362 sexually active women aged 15 - 49 years who participated in the Nigeria 2003 Demographic and Health Survey using multilevel logistic regression models. Results are presented as odds ratio with 95% confidence interval. Independent of other factors, compared to women aged 15-24 years, those 25 - 34 years (odds ratio [OR] 0.59; 95% CI: 0.44 - 0.79) and 35 years or older (OR 0.36; 95% CI: 0.24 - 0.54) were less likely to have reported multiple concurrent sex partners in the last 12 years. As expected, women currently or formerly married were less likely to have reported multiple concurrent sex partners than women never married. Women who drank alcohol in the last three months were more likely to have reported multiple concurrent sex partners. Compared to women from richest household, women from poorest and middle household were 83% and 51% more likely to have multiple concurrent sex partners in the last 12 month respectively. After individual compositional and contextual factors, community wealth status was statistically significant with sexual behaviour. The study has demonstrated that individual and community wealth status are independent predictors of women's sexual behaviour, and that there is significant neighbourhood variation in odds of multiple concurrent sex partners, even after controlling for effects of both individual- and community-level characteristics. Scholars trying to understand variation individual high risk sexual behaviour should pay attention to the characteristics of both individuals and places of residence. **Editors' note: Although this study has a large sample size, it suffers from its vague definition of the high-risk sexual behaviour 'multiple concurrent partners'. This is defined as 'having two or more sex partners in the last 12 months'. Such a definition lumps together women who became widows or divorced or left a partnership earlier in the year and then entered a new partnership (with no concurrency), women who exchange sex for money at high frequency (possibly with no concurrency, depending on your definition, unless they have regular clients or an ongoing boyfriend/husband), and women with concurrent partnerships. It makes sense that sexually active unmarried women, women who drink alcohol, or women from poor or middle-income households, are more likely to have two or more partners in the previous 12 months but no evidence is presented to suggest that these are concurrent partnerships, let alone 'multiple' concurrent partnerships.**

## 5. *Drug resistance*

Johnson JA, Li J-F, Wei X, Lipscomb J, Irlbeck D, Craig C, Smith A, Bennett DE, Monsour M, Sandstrom P, Lanier ER, Heneine W. Minority HIV-1 drug resistance mutations are present in antiretroviral treatment-naïve populations and associate with reduced treatment efficacy. *PLoS Medicine* July 2008(5); 7:e158

Transmitted HIV-1 drug resistance can compromise initial antiretroviral therapy (ART); therefore, its detection is important for patient management. The absence of drug-associated selection pressure in treatment-naïve persons can cause drug-resistant viruses to decline to levels undetectable by conventional bulk sequencing (minority drug-resistant variants). They used sensitive and simple tests to investigate evidence of transmitted drug resistance in antiretroviral drug-naïve persons and assess the clinical implications of minority drug-resistant variants. Johnson et al performed a cross-sectional analysis of transmitted HIV-1 drug resistance and a case control study of the impact of minority drug resistance on

treatment response. For the cross-sectional analysis, they examined viral RNA from newly diagnosed ART-naïve persons in the US and Canada who had no detectable (wild type, n=205) or one or more resistance-related mutations (n=303) by conventional sequencing. Eight validated real-time PCR-based assays were used to test for minority drug resistance mutations (protease L90M and reverse transcriptase M41L, K70R, K103N, Y181C, M184V, and T215F/Y) above naturally occurring frequencies. The sensitive real-time PCR testing identified one to three minority drug resistance mutation(s) in 34/205 (17%) newly diagnosed persons who had wild-type virus by conventional genotyping; four (2%) individuals had mutations associated with resistance to two drug classes. Among 30/303 (10%) samples with bulk genotype resistance mutations they found at least one minority variant with a different drug resistance mutation. For the case-control study, they assessed the impact of three treatment-relevant drug resistance mutations at baseline from a separate group of 316 previously ART-naïve persons with no evidence of drug resistance on bulk genotype testing who were placed on efavirenz-based regimens. Johnson et al found that 7/95 (7%) persons who experienced virologic failure had minority drug resistance mutations at baseline; however, minority resistance was found in only 2/221 (0.9%) treatment successes (Fisher exact test,  $p < 0.0038$ ). These data suggest that a considerable proportion of transmitted HIV-1 drug resistance is undetected by conventional genotyping and that minority mutations can have clinical consequences. With no treatment history to help guide therapies for drug-naïve persons, the findings suggest an important role for sensitive baseline drug resistance testing. **Editors' note: Conventional bulk sequencing resistance testing detects resistant viruses when they start to reach the level of 20% of all HIV viruses in an infected person. It may miss the presence of minority resistant viruses in up to 17% of newly diagnosed antiretroviral treatment-naïve persons. However, this study using highly sensitive PCR testing revealed that only 7% of those who experienced antiretroviral treatment (ART) failure, in retrospect, had evidence of undetectable viral resistance at baseline. Nevertheless, concerted efforts are needed to keep first-line ART as effective as possible and to prevent HIV transmission, whether from ART-experienced or ART-naïve people.**

## 6. Economics

Souteyrand YP, Collard V, Moatti JP, Grubb I, Guerma T. Free care at the point of service delivery: a key component for reaching universal access to HIV/AIDS treatment in developing countries. *AIDS*. 2008 Jul;22 Suppl 1:S161-8.

User fees are a common feature of health system financing in low and middle-income countries. In the context of universal access to HIV treatment and care, the advantages of user fees for funding at country and local level should be balanced with their clinical and public health impact. Souteyrand et al reviewed the literature on user fees and the impact of user fees on HIV service delivery. Empirical evidence gathered since the 1980s shows that sustainability, efficiency and equity challenges faced by health systems have persisted with and have often been exacerbated by the introduction of user fees. The evidence on HIV suggests that free care at the point of service fosters uptake and helps to extend access for the poorest users. User fees are currently the main barrier to adherence to antiretroviral therapy. Their abolition is associated with better virological results and increased survival. Such abolition should be carried out in parallel with the implementation of financing mechanisms, such as prepayment and risk pooling, which are able to gather funds from the sectors of the population who are able to pay for healthcare and to promote equity

towards the poorest. WHO has included free access to HIV treatment at the point of service delivery as a component of its public health approach for reaching universal access. Implementation of free HIV care should, however, be linked to efforts to strengthen healthcare systems, ensure long-term sustainability of funding and monitor equity of access to care. **Editors' note: Financial barriers cannot be allowed to provoke non-adherence and compromise first-line treatment regimens. In March 2005, countries were advised to adopt a policy of free access to HIV treatment at the point of service delivery, following a WHO/UNAIDS/World Bank consultation. Abolition of user fees and introduction or strengthening of more equitable funding mechanisms can create positive spillover that increases access and strengthens health care infrastructure as a whole.**

Beck EJ, Santas XM and DeLay PR. Why and how to monitor the cost and evaluate the cost-effectiveness of HIV services in countries. *AIDS* 2008, 22 (suppl 1):S75-S85

The number of people in the world living with HIV is increasing as HIV-related mortality has declined but the annual number of people newly infected with HIV has not. The international response to contain the HIV pandemic, meanwhile, has grown. Since 2006, an international commitment to scale up prevention, treatment, care and support services in middle and lower-income countries by 2010 has been part of the Universal Access programme, which itself plays an important part in achieving the Millennium Development Goals by 2015. Apart from providing technical support, donor countries and agencies have substantially increased their funding to enable countries to scale up HIV services. Many countries have been developing their HIV monitoring and evaluation systems to generate the strategic information required to track their response and ensure the best use of the new funds. Financial information is an important aspect of the strategic information required for scaling up existing services as well as assessing the effect of new ones. It involves two components: tracking the money available and spent on HIV at all levels, through budget tracking, national health accounts and national AIDS spending assessments, and estimating the cost and efficiency of HIV services. The cost of service provision should be monitored over time, whereas evaluations of the cost-effectiveness of services are required periodically; both should be part of any country's HIV monitoring and evaluation system. This paper provides country examples of the complementary relationship between monitoring the cost of HIV services and evaluating their cost-effectiveness. It also summarizes global initiatives that enable countries to develop their own HIV monitoring and evaluation systems and to generate relevant, robust and up-to-date strategic information. **Editors' note: If you have been lost in the jargon, this paper sorts out the differences between effectiveness (outcome or impact of programmes or services), efficiency (resources require to achieve a certain outcome or impact), equity (who benefits from programmes or services), and acceptability (both to users and providers of services and in terms of improvements in the quality of life that programmes achieve). These criteria are supported by other pieces of strategic information that underpin a plan of action for programmes or services, such as direct and indirect costs and HIV incidence/prevalence. Topping this off with a robust monitoring and evaluation system, similar to those that many countries are now developing, can enhance country responses.**

## **7. Paediatrics**

Giaquinto C, Morelli E, Fregonese F, Rampon O, Penazzato M, de Rossi A, D'Elia R. Current and future antiretroviral treatment options in paediatric HIV infection. Clin Drug Investig. 2008;28(6):375-97. PMID: 18479179 [PubMed - in process]

Because of a lack of prevention policies or problems in implementing prevention of mother-to-child transmission (P-MTCT), most of the 1500 daily new HIV infections in children aged <15 years are caused by MTCT. Fifteen percent of all HIV-infected individuals are children, but the vast majority lack access to highly active antiretroviral therapy (HAART), which can drastically reduce morbidity and mortality. There are 22 antiretroviral drugs currently approved by the US FDA for use in the treatment of HIV-infected adults and adolescents, but only 12 of these drugs are approved for use in children. Antiretroviral drugs belong to four major classes: nucleoside and nucleotide analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors and fusion inhibitors. According to international guidelines developed by organizations including WHO, the Paediatric European Network for Treatment of AIDS (PENTA) and the US National Institutes of Health (US-NIH), the treatment of choice for HIV-infected children and adults is a combination of two NRTIs (backbone treatment) plus a third potent agent from a different class, either an NNRTI or a ritonavir-boosted protease inhibitor. There are specific challenges in treating HIV-infected children, including uncertainty about the best time to start treatment, the need for more paediatric formulations, the lack of pharmacokinetic studies for new drugs, and incomplete dosing guidelines. Furthermore, the most appropriate regimen for an individual child depends on a variety of factors, including the age of the child; the availability of appropriate drug formulations; the potency, complexity and toxicity of the drug regimen; the home situation; the child and caregiver's ability to adhere to the regimen; and the child's antiretroviral treatment history. In addition, antiretroviral drugs are not licensed for all age groups and the drugs are often not affordable. This review describes NNRTI and protease inhibitors as key components of first- and second-line antiretroviral therapy (ART), focusing on the rationale for choosing an NNRTI- versus protease inhibitor-based regimen based on the results of available phase II and III studies. Some of the new agents available for children as second-line and salvage therapy both on- and off-label are also discussed. The drug regimens described in this review are relevant to clinicians in developed and developing countries. The availability of new, potent compounds with different resistance and toxicity profiles may represent an alternative option to interclass switching and could redefine ART strategy, including the option of first-line NRTI-sparing regimens. **Editors' note: WHO has recommended the development of new paediatric fixed-dose combinations containing NNRTIs and protease inhibitors to increase the availability of affordable, safe, and effective formulations for children. With one in every six or seven people living with HIV today being a child under 15 years of age, it is imperative that we increase therapeutic options for children.**

Van Rie A, Mupuala A, Dow A. Impact of the HIV/AIDS epidemic on the neurodevelopment of preschool-aged children in Kinshasa, Democratic Republic of the Congo. 198: Pediatrics. 2008 Jul;122(1):e123-8. 198.

Paediatric HIV infection is a growing problem in most regions of the world. Data on the effects of HIV on the neurodevelopment of children in resource-poor settings are scarce but necessary to guide interventions. The purpose of this study was to compare the neurodevelopment of preschool-aged HIV-infected, HIV-affected (HIV-uninfected AIDS

orphans and HIV-uninfected children whose mother had symptomatic AIDS), and healthy control children in Kinshasa, Democratic Republic of Congo. In this study thirty-five HIV-infected, 35 HIV-affected, and 90 control children aged 18 to 72 months were assessed by using the Bayley Scales of Infant Development II, Peabody Developmental Motor Scales, Snijders-Oomen Nonverbal Intelligence Test, and Rossetti Infant-Toddler Language Scale, as appropriate for age. Overall, 60% of HIV-infected children had severe delay in cognitive function, 29% had severe delay in motor skills, 85% had delays in language expression, and 77% had delays in language comprehension, all significantly higher rates as compared with control children. Young HIV-infected children (aged 18-29 months) performed worse, with 91% and 82% demonstrating severe mental and motor delay, respectively, compared with 46% and 4% in older HIV-infected children (aged 30-72 months). HIV-affected children had significantly more motor and language expression delay than control children. The impact of the HIV pandemic on children's neurodevelopment extends beyond the direct effect of the HIV virus on the central nervous system. AIDS orphans and HIV-negative children whose mothers had AIDS demonstrated significant delays in their neurodevelopment, although to a lesser degree and in fewer developmental domains than HIV-infected children. Young HIV-infected children were the most severely afflicted group, indicating the need for early interventions. Older children performed better as a result of a "survival effect," with only those children with less aggressive disease surviving. **Editors' note: Delayed neurodevelopment is a well-recognised complication of HIV disease. Central nervous system involvement can be the AIDS-defining illness in almost one in five paediatric patients. These results from Kinshasa suggest that HIV is affecting child neurodevelopment through both the direct effect of HIV on the central nervous system and its effect on the child's living conditions (family poverty, poor health, and fewer positive parent-child interactions conducive to a child's neurodevelopment). Early identification and provision of nutritional and care programmes for vulnerable children (infected and affected) can contribute to their well-being and stimulate their mental and motor development.**

### **8. Men who have sex with men**

Cáceres CF, Aggleton P, Galea JT. Sexual diversity, social inclusion and HIV/AIDS. AIDS. 2008 Aug;22 Suppl 2:S45-55.

Despite a number of programmes to prevent HIV among men who have sex with men (MSM) and, more generally, sexually diverse populations, gay and other homosexually active men continue to be at heightened risk of HIV and its consequences. This paper analyses some of the reasons for this situation and offers policy and programmatic recommendations to contribute to a solution. The social exclusion of MSM and transgender individuals is an overwhelming reality in the majority of countries worldwide. Although progress has been achieved in some countries, in most of the world the situation remains problematic. Present challenges to equality and to the realization of health, include the membership of groups or subcultures with high HIV prevalence, lower quality and coverage of services and programmes and the impact of higher-level influences such as laws, public policies, social norms and culture, which together configure an environment that is hostile to the integration and needs of certain groups. A social inclusion perspective on HIV prevention and AIDS-related care implies the adoption of strategies to understand and confront social vulnerability. Sexual exclusion intensifies the burden of HIV transmission and morbidity. As

part of a comprehensive response there is an urgent need to: (i) improve our understanding of the characteristics and HIV burden among sexually diverse populations; (ii) creatively confront legal, social and cultural factors enhancing sexual exclusion; (iii) ensure the provision of broad-based and effective HIV prevention; (iv) offer adequate care and treatment; and (v) confront special challenges that characterize work with these populations in lower and middle-income countries. **Editors' note: Sexual diversity is a term that questions 'heteronormativity', challenging the assumption that there is a single sexual normality and affirming the value of different forms of sexual expression. Sexual behaviour, sexual identity, and gender identify vary significantly across cultures and this complexity argues strongly for participatory prevention programmes - a 'nothing about us without us' inclusivity principle that is key to effective programming. Anchoring this approach in commitment to protect and uphold human rights can help overcome the legal, societal, and cultural barriers which create exclusion and undermine HIV programming.**

### ***9. Structural determinants and approaches***

Gupta GR, Parkhurst JO, Ogden JA, Aggleton P, Mahal A. Structural approaches to HIV prevention. *Lancet*. 2008 Aug 30;372(9640):764-75. Epub 2008 Aug 5.

Recognition that social, economic, political, and environmental factors directly affect HIV risk and vulnerability has stimulated interest in structural approaches to HIV prevention. Progress in the use of structural approaches has been limited for several reasons: absence of a clear definition; lack of operational guidance; and limited data on the effectiveness of structural approaches to the reduction of HIV incidence. In this paper Gupta et al build on evidence and experience to address these gaps. They begin by defining structural factors and approaches. Structural factors include the physical, social, cultural, organisational, community, economic, legal, or policy features of the environment that affect HIV infection. These factors operate at different societal levels and different distances to influence individual risk and to shape social vulnerability to infection. Structural approaches to HIV prevention seek to change social, economic, political, or environmental factors determining HIV risk and vulnerability. They should be implemented in a contextually sensitive way, in recognition of both the need for situational relevance and the interaction between different levels of influence. Gupta et al describe the available evidence on their effectiveness and discuss methodological challenges to the assessment of these often complex efforts to reduce HIV risk and vulnerability. They identify core principles for implementing this kind of work. They also provide recommendations for ensuring the integration of structural approaches as part of combined prevention strategies. **Editors' notes: Broad structural factors such as poverty and wealth, gender inequality, age, social marginalisation, laws and policies, and power both shape and constrain individual behaviour. They can be distal (further way from risk-taking, e.g. the economy) or proximal (more directly influencing risk, e.g. personal unemployment). They can undermine HIV prevention programmes that are narrowly focused on individuals. Combining structural approaches that aim to change the social, economic, or environmental factors that determine HIV risk and vulnerability in specified contexts with behavioural or biomedical prevention programmes not only increases programme effectiveness, it can transform social norms to support sustained behaviour change.**

### ***10. Prevention***

Coates TJ, Richter L, Caceres C. Behavioural strategies to reduce HIV transmission: how to make them work better. *Lancet*. 2008 Aug 23;372(9639):669-84. Epub 2008 Aug 5.

This paper makes five key points. First is that the aggregate effect of radical and sustained behavioural changes in a sufficient number of individuals potentially at risk is needed for successful reductions in HIV transmission. Second, combination prevention is essential since HIV prevention is neither simple nor simplistic. Reductions in HIV transmission need widespread and sustained efforts, and a mix of communication channels to disseminate messages to motivate people to engage in a range of options to reduce risk. Third, prevention programmes can do better. The effect of behavioural strategies could be increased by aiming for many goals (e.g. delay in onset of first intercourse, reduction in number of sexual partners, increases in condom use, etc) that are achieved by use of multilevel approaches (e.g. couples, families, social and sexual networks, institutions, and entire communities) with populations both uninfected and infected with HIV. Fourth, prevention science can do better. Interventions derived from behavioural science have a role in overall HIV-prevention efforts, but they are insufficient when used by themselves to produce substantial and lasting reductions in HIV transmission between individuals or in entire communities. Fifth, we need to get the simple things right. The fundamentals of HIV prevention need to be agreed upon, funded, implemented, measured, and achieved. That, presently, is not the case. **Editors' note: Behavioural change has been responsible for prevention successes at community level but it has not happened in a vacuum. Social change to avoid risk has occurred when the community is mobilised and engaged in message design, production, and dissemination; when messages have been simple, clear, and present choices for individuals and couples; and when people have access to prevention tools and services (e.g. male and female condoms, sterile needles and syringes, and HIV testing) to follow through on their intentions to protect themselves and others. 'Doing better' at achieving HIV prevention in a comprehensive and sustained manner is an imperative - HIV is for life but it is preventable.**

## 11. Treatment

Laureillard D, Prak N, Fernandez M, Ngeth C, Moeung S, Riel V, Chhneang V, Song S, Quillet C and Piketty C. Efavirenz replacement by immediate full-dose nevirapine is safe in HIV-1-infected patients in Cambodia. *HIV Medicine* 2008; DOI: 10.1111/j.1468-1293.2008.00597.x

Efavirenz is used for the antiretroviral treatment of HIV/tuberculosis-coinfected patients in developing countries. A switch to nevirapine is regularly carried out because of the cost and side effects of efavirenz. Pharmacokinetic studies suggested that nevirapine should be initiated at full dose when used as a substitute for efavirenz. The aim of this study was to measure the cumulative incidence of adverse events (AEs) related to nevirapine in patients switched from efavirenz to immediate full-dose nevirapine (FDN). In 2001 an antiretroviral treatment programme was initiated with the first-line regimen stavudine, lamivudine and efavirenz. In 2003, the fixed-dose combination of stavudine, lamivudine and nevirapine was recommended. Thus, first-line therapy was changed and FDN was initiated when patients were switched from efavirenz to nevirapine. Between April and December 2004, 394 patients were switched from efavirenz to full does nevirapine. The cumulative incidence of AEs related to nevirapine was 13.2% [95% confidence interval (CI) 10.2- 16.7] and that of severe AEs was 8.9% (95% CI 6.5-11.9). In women the incidence of AEs was 17.6% (95% CI 12.1-24.3) and that of severe AEs was 12.2% (95% CI 7.7-18.2). Laureillard et al's results

indicate that a full dose nevirapine switch from efavirenz does not appear to result in more adverse events than when nevirapine is initiated with escalating doses. These data are particularly relevant in resource-limited settings. **Editors' note: Efavirenz is more expensive than nevirapine, should not be used in women of childbearing potential, and has a long plasma half-life. This is the first study evaluating a switch from an efavirenz-containing regimen to a nevirapine-containing one where full-dose nevirapine rather than escalating doses of nevirapine were used to overcome efavirenz competition for cytochrome CYP 3A4 and reduce the risk of nevirapine resistance. It is encouraging that increased adverse effects were not seen.**

## 12. Epidemiology

Stover J, Johnson P, Zaba B, Zwahlen M, Dabis F and Ekpini RE. The Spectrum projection package: improvements in estimating mortality, ART needs, PMTCT impact and uncertainty bounds. *Sex. Transm. Inf.* 2008;84;i24-i30

The approach to national and global estimates of HIV used by UNAIDS starts with estimates of adult HIV prevalence prepared from surveillance data using either the Estimation and Projection Package (EPP) or the Workbook. Time trends of prevalence are transferred to Spectrum to estimate the consequences of the HIV epidemic, including the number of people living with HIV, new infections, AIDS deaths, AIDS orphans, treatment needs and the impact of treatment on survival. The UNAIDS Reference Group on Estimates, Modelling and Projections regularly reviews new data and information needs and recommends updates to the methodology and assumptions used in Spectrum. The latest update to Spectrum was used in the 2007 round of global estimates. Several new features have been added to Spectrum in the past two years. The structure of the population was reorganised to track populations by HIV status and treatment status. Mortality estimates were improved by the adoption of new approaches to estimating non-AIDS mortality by single age, and the use of new information on survival with HIV in non-treated cohorts and on the survival of patients on antiretroviral treatment. A more detailed treatment of mother-to-child transmission of HIV now provides more prophylaxis and infant feeding options. New procedures were implemented to estimate the uncertainty around each of the key outputs. The latest update to the Spectrum programme is intended to incorporate the latest research findings and provide new outputs needed by national and international planners **Editors' note: This article provides excellent background on the inner workings and assumptions of the Spectrum projection package, that continues to evolve as new evidence comes forward and new procedures are introduced. These include new information on mortality from long-running cohorts and the effects of antiretroviral treatment on survival, as well as adjustments to better estimate uncertainty around the estimates. These refinements are increasing our understanding of the scope and magnitude of the HIV epidemic and are helping plan more effective responses at both national and international levels.**

Tee KK, Pybus OG, Li XJ, Han X, Shang H, Kamarulzaman A, Takebe Y. Temporal and Spatial Dynamics of the Human Immunodeficiency Virus Type 1 Circulating Recombinant Forms O8\_BC and O7\_BC in Asia. 168: *J Virol.* 2008 Jul 2. [Epub ahead of print]

Human immunodeficiency virus type 1 (HIV-1) CRF08\_BC and CRF07\_BC are two major recombinants descended from subtypes B' and C. Despite their massive epidemic impact in China, their migration patterns and divergence times remain unknown. Phylogenetic and

population genetic analyses were performed on 228 HIV-1 sequences, representing CRF08\_BC, CRF07\_BC and subtype C strains from different locations across China, India and Myanmar. Genome-specific rates of evolution and divergence times were estimated using a Bayesian MCMC framework under various evolutionary models. CRF08\_BC originated in 1990.3 (95% credible region, CR: 1988.6-1991.9) in Yunnan province, before spreading to Guangxi (south) and Liaoning (northeast) around 1995. Inside Guangxi region, the eastward expansion of CRF08\_BC continued from Baise city (west) to Binyang (central) between 1997 and 1998, and later spread into Pingxiang around 1999 in the south, mainly through injecting drug use. Additionally, CRF07\_BC diverged from its common ancestor in 1993.3 (95% CR: 1991.2-1995.2) before crossing the border into southern Taiwan in late 1990s. Phylogenetic analysis indicates that both CRF08\_BC and CRF07\_BC can trace their origin to Yunnan. The parental Indian subtype C lineage likely entered China around 1981.2 (95% CR: 1976.7-1985.9). Using multiple unlinked loci model, we also showed that the dates of divergence calculated in this study may not be significantly affected by intrasubtype recombination among different lineages. This is the first phylodynamic study depicting the spatiotemporal dynamics of HIV/AIDS in East Asia. **Editors' note: Yunnan, located in south-western China, borders on the 'Golden Triangle' of south-east Asia, one of the world's largest heroin producing regions. It is considered to be an epicentre of HIV in China - the first case was detected there in 1989. Recombination, an intrinsic evolutionary mechanism that shapes HIV diversity, creates a footprint that permits tracking of HIV transmission over time and through space. Genealogical analysis of these footprints reconstructs the epidemiological history of viral populations, enhancing understanding of HIV transmission to improve prevention programming.**

Azim T, Rahman M, Alam MS, Chowdhury IA, Khan R, Reza M, Rahman M, Chowdhury EI, Hanifuddin M, Rahman AS. Bangladesh moves from being a low-prevalence nation for HIV to one with a concentrated epidemic in injecting drug users. *Int J STD AIDS*. 2008 May;19(5):327-31. PMID: 18482963 [PubMed - in process]

Bangladesh has been conducting annual serological surveillance for HIV and syphilis since 1998 among most at-risk populations including sex workers, males having sex with males, injecting drug users (IDUs) and heroin smokers. During the seventh round conducted between January and June 2006, 10,368 people were sampled and the overall HIV prevalence was 0.9%. The highest HIV rate was recorded in male IDUs from the capital city Dhaka (7%), and the rates have risen significantly over the rounds (P < 0.001). In Dhaka, most of the HIV-positive IDUs (10.5%) were localized in one neighbourhood, while in the remaining neighbourhoods 1% were positive (P < 0.001). In all other groups, HIV prevalence was <1%. Active syphilis rates were highest in female IDUs (9.9%) followed by female street-based sex workers (8.6%). However, rates in female sex workers in Dhaka declined significantly over the years (P < 0.001). Bangladesh has to act urgently to prevent escalation of the epidemic. **Editors' note: Bangladesh's move from a low prevalence to a concentrated epidemic has been slow but predictable, given documented ongoing risk among populations at highest risk of HIV exposure, particularly injecting drug users (IDU). Localisation of the concentrated IDU epidemic in one neighbourhood gives hope that a focused effort to provide more intensive comprehensive and effective harm reduction services to this neighbourhood, with diffusion outward to IDU throughout the country, could help turn the epidemic in this population around.**

That was *HIV this week*, signing off.

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