

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

Welcome to the 72<sup>nd</sup> issue of *HIV This Week*! Many thanks to all of you who completed our recent survey. You gave us excellent suggestions for improvements and we will be introducing a number of changes in upcoming issues. In this issue, we cover *monitoring and evaluation* (how burial surveillance revealed steep declines in population-level AIDS mortality in Addis Ababa, Ethiopia; what is the delay nationwide between HIV diagnosis and first consultation for treatment in Cameroon?), *adolescents* (perinatally infected adolescents in Uganda come of age: sexual behaviour and desires; a trial of 'teachable moment' group HIV prevention interventions among criminally involved 14 to 17 years olds in detention), *basic science* (there are two distinct HIV reservoirs), *treatment* (long-acting injectables: the wave of the future?; why you should avoid insects if you are taking a CCR5 antagonist; how safe is once daily nevirapine?), *sex work* (condoms and negotiation skills training needed for male sex workers in Mumbai, India; toward safer sex work conditions for women in Vancouver, Canada: why legal and policy changes are needed to overcome structural and environmental barriers to condom use negotiation), *communications and stigma* (impact of HIV campaigns on accepting attitudes to people living with HIV in Nigeria), *morbidity and co-morbidity* (deaths due to cryptococcal meningitis may exceed those due to TB in sub-Saharan Africa; autopsies reveal missed diagnoses in HIV-related deaths in Liverpool), *sexual and reproductive health* (a systematic review of fertility desires and intentions reveals that health care workers in virtually all cultures are missing the boat; why reproductive health and HIV care services need to be integrated in Cape Town, South Africa), *vaccine vectors* (lentiviral vectors may prove useful for HIV vaccine design; a recombinant adenovirus shot in the gut to enhance mucosal cellular immunity?), and *prevention of mother-to-child transmission* (time for nationwide services in Haiti; how intrauterine growth retardation due to maternal HIV can be prevented in Thailand).

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## 1. *Monitoring and Evaluation*

Reniers G, Araya T, Davey G, Nagelkerke N, Berhane Y, Coutinho R, Sanders EJ. Steep declines in population-level AIDS mortality following the introduction of antiretroviral therapy in Addis Ababa, Ethiopia. *AIDS*. 2009;23:511-518.

Assessments of population-level effects of antiretroviral therapy programmes in Africa are rare. Reniers and colleagues use data from burial sites to estimate trends in adult AIDS mortality and the mitigating effects of antiretroviral therapy in Addis Ababa. Antiretroviral therapy has been available since 2003, and for free since 2005. To substitute for deficient vital registration, the authors use surveillance of burials at all cemeteries. They present trends in all-cause mortality, and estimate AIDS mortality (ages 20-64 years) from lay reports of causes of death. These lay reports are first used as a diagnostic test for the true cause of death. As reference standard, the authors use the cause of death established via verbal autopsy interviews conducted in 2004. The positive predictive value and sensitivity are subsequently used as anchors to estimate the number of AIDS deaths for the period 2001-2007. Estimates are compared with Spectrum projections. Between 2001 and 2005, the number of AIDS deaths declined by 21.9% and 9.3% for men and women, respectively. Between 2005 and 2007, the number of AIDS deaths declined by 38.2 for men and 42.9% for women. Compared with the expected number in the absence of antiretroviral therapy, the reduction in AIDS deaths in 2007 is estimated to be between 56.8% and 63.3%, depending on the coverage of the burial surveillance. Five years into the antiretroviral therapy programme, adult AIDS mortality has been reduced by more than half. Following the free provision of antiretroviral therapy in 2005, the decline accelerated and became more sex balanced. Substantial AIDS mortality, however, persists. **Editors' note: When vital registration systems do not function well enough to provide accurate cause-specific adult mortality estimates, burial surveillance can provide data for realistic estimates of the impact of antiretroviral treatment programmes. During 2003-2005, the Ethiopian national programme required a co-payment of 28-80USD per month and AIDS mortality fell 15.8% in Addis Ababa, more in men than in women. The decline was far sharper between 2005 and 2007 (40.6%) when antiretroviral treatment was free, with greater declines observed for women. This study demonstrates the utility of using other information sources to monitor programme effects when vital registration is deficient and suggests a restraining effect of co-payments on antiretroviral treatment uptake, particularly for women who may have less access to resources for financing treatment.**

Marcellin F, Abé C, Loubière S, Boyer S, Blanche J, Koulla-Shiro S, Ongolo-Zogo P, Moatti JP, Spire B, Carrieri MP; and the EVAL Study Group. Delayed first consultation after diagnosis of HIV infection in Cameroon. *AIDS*. 2009;23:1015-1019.

Marcellin and colleagues set out to study the impact of both decentralization of HIV care and individual factors on delayed first consultation (>=6 months) after HIV diagnosis in Cameroon, in the context of the national antiretroviral treatment scale-up program. The national cross-sectional multicenter survey EVAL (ANRS 12-116) was conducted from September 2006 to March 2007 in 27 HIV centres in Cameroon. Logistic regression was used to characterize patients with delayed first consultation among 3151 HIV-infected adults. Fifteen percent of patients reported a delay of at least 6 months before their first consultation after HIV diagnosis. In the multivariate analysis adjusted for the frequency of

visits to the HIV centre, independent correlates of reporting a delay of at least 6 months before consulting included the characteristics of the HIV centres (created before 2005 and located in small or medium-size hospitals) and the following individual patient characteristics: sex and matrimonial status (women living in a couple), the circumstances of the HIV diagnosis (test not performed in the hospital providing HIV care, test performed during a voluntary screening campaign) and patient's negative perception of antiretroviral treatment toxicity. Delays before first consultation for HIV care in Cameroon have been reduced, thanks to the full implementation of the national program of decentralization. Results underline the importance of coordinating diagnosis with treatment activities and the need to develop counselling actions, focusing on the balance between antiretroviral treatment effectiveness and its potential side effects. Counselling should also be part of patients' follow-up after diagnosis during voluntary screening campaigns. **Editors' note: This is the first nation-wide study in sub-Saharan Africa to explore components of the causal process leading to late access to antiretroviral treatment: late HIV diagnosis versus delayed first consultation after HIV diagnosis. Decentralisation of HIV services in Cameroon has had the benefit of more prompt access to care, with 57% of patients experiencing a delay of less than 1 month between HIV diagnosis and their first medical consultation for HIV care. With many of the factors influencing delayed onset of antiretroviral treatment highlighted by this study, now programme planners and implementers can introduce modifications to reduce the delay. Their focus should be on the 15% who are not assessed for antiretroviral treatment until 6 months or more after HIV diagnosis and those who are lost to follow-up after an initial HIV diagnosis.**

## 2. Adolescents

Birungi H, Mugisha JF, Obare F, Nyombi JK. Sexual behaviour and desires among adolescents perinatally infected with human immunodeficiency virus in Uganda: implications for programming. *J Adolesc Health*. 2009;44:184-7.

Counselling programs for adolescents living with human immunodeficiency virus (HIV) encourage abstinence from sex and relationships. This Uganda study, however, found that many of these adolescents are sexually active or desire to be in relationships but engage in poor preventive practices. Programmes for HIV therefore need to strengthen preventive services to this group. **Editors' note: In this study, 732 adolescents aged 15 to 19 years living with HIV in 4 districts in Uganda were interviewed, 48 participated in focus group discussions, and 12 underwent in-depth interviews for ethnographic case stories. One-third was sexually active and of these 38% had disclosed their HIV status to their current partners. Overall 51% feared disclosing their status to their friends. At first sex, 37% had used condoms and much of current condom use was for pregnancy prevention. Clearly, the sexual and reproductive needs of this unique and growing population of perinatally infected young people are not being adequately met by current service approaches.**

Schmiege SJ, Broaddus MR, Levin M, Bryan AD. Randomized trial of group interventions to reduce HIV/STD risk and change theoretical mediators among detained adolescents. *J Consult Clin Psychol*. 2009;77:38-50.

Criminally involved adolescents engage in high levels of risky sexual behaviour and alcohol use, and alcohol use may contribute to lack of condom use. Detained adolescents (n = 484) were randomized to (1) a theory-based sexual risk reduction intervention (GPI), (2) the GPI

condition with a group-based alcohol risk reduction motivational enhancement therapy component (GPI + GMET), or (3) an information-only control (INFO). All interventions were presented in same-sex groups in single sessions lasting from 2 to 4 hr. Changes to putative theoretical mediators (attitudes, perceived norms, self-efficacy, and intentions) were measured immediately following intervention administration. The primary outcomes were risky sexual behaviour and sexual behaviour while drinking measured 3 months later (65.1% retention). The GPI + GMET intervention demonstrated superiority over both other conditions in influencing theoretical mediators and over the INFO control in reducing risky sexual behaviour. Self-efficacy and intentions were significant mediators between condition and later risky sexual behaviour. This study contributes to an understanding of harm reduction among high-risk adolescents and has implications for understanding circumstances in which the inclusion of group-based alcohol risk reduction motivational enhancement therapy components may be effective.

**Editors' note: Criminally involved adolescents in detention present challenges to effective HIV prevention on several levels but this is, after all, a 'teachable moment' when they may more easily contemplate the negative aspects of a behaviour as well as avenues of behaviour change. Most of the 14 to 17 year olds (82.7% male) in this study were sexually active (92.7%) with a median age at first intercourse of 13.02 years. Of these, 82% reported alcohol use during a sexual encounter. In the full group, 90.9% had used alcohol in the past year with the average number of drinks at one time being 4.7. This randomised controlled trial found that incorporating an alcohol-related sexual risk reduction component that was non-confrontational and supportive into a more traditional sexual risk reduction intervention resulted in increased condom use self-efficacy and intentions to use condoms. Retention at 3 months was low but nonetheless these promising findings deserve further study and practical application.**

### **3. Basic science**

Chomont N, El-Far M, Ancuta P, Trautmann L, Procopio FA, Yassine-Diab B, Boucher G, Boulassel MR, Ghattas G, Brenchley JM, Schacker TW, Hill BJ, Douek DC, Routy JP, Haddad EK, Sékaly RP. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. *Nat Med.* 2009;15:893-900.

HIV persists in a reservoir of latently infected CD4(+) T cells in individuals treated with highly active antiretroviral therapy (HAART). Here Chomont and colleagues identify central memory (T(CM)) and transitional memory (T(TM)) CD4(+) T cells as the major cellular reservoirs for HIV and find that viral persistence is ensured by two different mechanisms. HIV primarily persists in T(CM) cells in subjects showing reconstitution of the CD4(+) compartment upon HAART. This T-cell central memory reservoir is maintained through T cell survival and low-level antigen-driven proliferation and is slowly depleted with time. In contrast, proviral DNA is preferentially detected in transitional memory t-cells from aviremic individuals with low CD4(+) counts and higher amounts of interleukin-7-mediated homeostatic proliferation, a mechanism that ensures the persistence of these cells. The authors conclude that their results suggest that viral eradication might be achieved through the combined use of strategic interventions targeting viral replication and, as in cancer, drugs that interfere with the self renewal and persistence of proliferating memory T cells.

**Editor's note: Early initiation of antiretroviral therapy is often associated with a reduced size of the HIV reservoir. Conversely, CD4 T-cell depletion associated with high levels of immune activation and increased proliferation tends to increase the size**

of the reservoir. The mechanisms underlying this have perplexed basic scientists for years. Chomont and colleagues have shed light on this by showing that there are two distinct HIV reservoirs. One is a long-lasting genetically stable reservoir found in immune responders to antiretroviral therapy that decays slowly and is regulated by antigen-driven proliferation. The second reservoir is genetically variable, predominates in people with low CD4 counts and persistent immune activation, and is regulated by homeostatic proliferation. The size of this second reservoir is reduced in individuals treated early in infection, supporting the concept of early initiation of antiretroviral treatment. The findings suggest that, beyond antiretroviral treatment, eradication of HIV in people with undetectable viral loads will require new therapies that target pathways downstream of proliferation such as those developed for treatment of leukaemia and cancer.

#### 4. Treatment

Baerta L, van 't Kloostera G, Dries W, François M, Wouters A, Basstanie E, Iterbeke K, Stappers F, Stevens P, Schueller L, Van Remoortere P, Kraus G, Wigerinck P, Rosier J. Development of a long-acting injectable with nanoparticles of rilpivirine (TMC278) for HIV treatment. *Eur J Pharm Biopharm.* 2009;72:502-508.

Long-acting parenteral formulations of antiretrovirals could facilitate maintenance and prophylactic treatment in HIV. Using the poorly water- and oil-soluble non-nucleoside reverse transcriptase inhibitor (NNRTI) TMC278 (rilpivirine) as base or hydrochloride (HCl), nanosuspensions were prepared by wet milling (Elan NanoCrystal® technology) in an aqueous carrier. Laser diffraction showed average particle sizes close to the targeted size proportionality (200-400-800 nm), with increasing distributions the larger the average particle size, and stable over 6 months. Following single-dose administration, the plasma concentration profiles showed sustained release of TMC278 over 3 months in dogs and 3 weeks in mice. On comparison of intramuscular and subcutaneous injection of 5 mg/kg (200 nm) in dogs, the subcutaneous route resulted in the most stable plasma levels (constant at 25 ng/mL for 20 days, after which declining slowly to 1-3 ng/mL at 3 months); 200 nm nanosuspensions achieved higher and less variable plasma concentration profiles than 400 and 800 nm nanosuspensions. In mice, the pharmacokinetic profiles after a single 20 mg/kg dose (200 nm) did not show relevant differences according to the surfactant used (poloxamer 338, or d-alpha-tocopheryl polyethylene glycol 1000 succinate). In conclusion, this study provides proof-of-concept that 200-nm sized TMC278 nanosuspensions may act as a long-acting injectable. **Editors' note: Injectable formulations of antiretroviral drugs for treatment would enhance adherence by reducing pill burden, would avoid the impact of food on drug bioavailability, and would limit the development of resistance by achieving sustained plasma concentrations, just as do injectable contraceptives and anti-psychotic drugs. This study in dogs and mice shows that nanosuspensions may be suitable as long-acting formulations. Interest in their development for pre-exposure prophylaxis (PrEP) purposes will grow if the current PrEP trials show promise.**

Telenti A. Safety concerns about CCR5 as an antiviral target. *Curr Opin HIV AIDS.* 2009;4:131-5.

Clinical trials of CCR5 antagonists attest to their efficacy and tolerance in HIV treatment. However, there has been debate on their long-term safety because of the role of CCR5 in innate immunity. This review highlights gaps in our understanding of epidemiology of

infections that are modulated by CCR5, in particular, in HIV-infected individuals. In the mouse model, CCR5 has a role in the response against pathogens as diverse as *Toxoplasma gondii*, West Nile virus, *Mycobacterium tuberculosis*, herpes simplex virus, *Trypanosoma cruzi*, *Cryptococcus neoformans*, *Chlamydia trachomatis*, *Listeria*, and plasmodia. In human cohorts, individuals carrying the defective CCR5Delta32 allele present an increased susceptibility to flavivirus (West Nile virus and tickborne encephalitis virus). The selective pressures that led to the spread of loss-of-function CCR5 mutations in humans (CCR5Delta32), and in mangabeys (CCR5Delta24) are not understood. The recent availability of CCR5 antagonists has raised concern that genetic, biological, or chemical CCR5 knockout, although beneficial against some pathogens (i.e. HIV), could be deleterious for other processes implicated in pathogen response. The consequences of long-term pharmaceutical intervention on CCR5 should be carefully assessed through rigorous postmarketing surveillance. **Editors' note: Although CCR5 delta 32 deletion appears to make people less likely to acquire HIV infection (if homozygous) and more likely to have slower HIV disease progression (if heterozygous), we do not know if interfering with this receptor's function pharmacologically with entry inhibitors that are CCR5 antagonists, such as maraviroc and vicriviroc, will have the same effects as congenital absence of the receptor. Because CCR5 appears to play a role in innate immunity against diverse diseases including trypanosomiasis, West Nile virus infection, malaria, and tick-borne encephalitis, it makes sense for people on CCR5 antagonists to limit their exposure to mosquitoes, ticks, and other biting insects until further information becomes available - we should all be trying to do this anyway.**

Podzamczar D, Olmo M, Sanz J, Boix V, Negredo E, Knobel H, Domingo P, Pineda JA, Vilades C, Quero JH, Force L, Lahoz JG, Muñoz P, Llibre JM, Mariño A, Ortega E, Dalmau D, Gatell JM, Antón E, Sola J, Galindo MJ, Pedrol E, Sanz J, de Lima JT, Flores J; the NODy Study Group. Safety of Switching Nevirapine Twice Daily to Nevirapine Once Daily in Virologically Suppressed Patients. *J Acquir Immune Defic Syndr*. 2009;50:390-396.

The strategy of switching nevirapine (NVP) twice daily to once daily was evaluated by means of a forty-eight-week randomized, open, multicentre trial. Stable HIV-infected patients on NVP twice daily for >12-18 weeks with alanine aminotransferase (ALT) <2.5, the upper normal limit were randomized to continue their regimen or switch to NVP 400 mg once daily. Primary end point was the proportion of ALT/aspartate transaminase (AST)  $\geq$  grade 3. Two hundred eighty-nine patients were included, mean CD4 620 cells per microliter. Noninferiority was demonstrated in the per protocol analysis, with 97.9% (once daily) and 99.3% (twice daily) of patients event free (difference, 1.4%; 95% confidence interval, -1.95% to 5.4%), whereas 81.8% vs. 93.8% were event free by intent-to-treat switch = toxicity analysis (difference, 12%; 95% confidence interval, 4.6% to 19.4%). Only 4 patients (3 once daily, 1 twice daily) had NVP-related grade  $\geq$  ALT/AST increases, but in 2 of them (once daily), transaminases decreased despite continuation with NVP. Two other once daily patients presented grade  $\geq$  ALT/AST increase due to well-documented acute hepatitis A virus or hepatitis C virus infection. Grade 2 ALT/AST increases occurred in 11.2% (once daily) vs. 10.3% (twice daily) of patients (P = 0.80). A larger number of once daily patients were lost to follow-up/violated protocol (15% vs. 5%). In patients on standard twice daily NVP-containing regimens for at least 12-18 weeks, per protocol analysis showed that switching to once daily NVP was not inferior to continued twice daily NVP in terms of the predefined noninferiority margin of 10% for hepatotoxicity. **Editors' note: Because once daily nevirapine (400 mg) may permit**

the design of simple once daily regimens that interfere less with daily activities, it is important to know whether it causes more toxicity than twice-daily 200 mg doses. Hypersensitivity to nevirapine in the form of liver toxicity usually presents in the first 12 to 18 weeks of treatment. If treatment guidelines are modified in the light of the findings of this and other studies, the switch to once daily nevirapine would likely not occur until after this initial period of twice-daily dosing. Independent risk factors for nevirapine-associated adverse events, such as gender, genetics, CD4 count, and hepatitis co-infection, remain considerations in prescribing antiretroviral regimens.

## 5. Sex work

Shinde S, Setia MS, Row-Kavi A, Anand V, Jerajani H. Male sex workers: are we ignoring a risk group in Mumbai, India? *Indian J Dermatol Venereol Leprol.* 2009;75:41-6.

Male sex workers have recently been recognized as an important risk group for sexually transmitted infections including human immunodeficiency virus infection. Although there are global studies on male sex workers, few such studies describe the behavioural patterns and sexually transmitted infections among this population in India. Male sex workers were evaluated at the Humsafar trust, a community based organization situated in suburban Mumbai, India. Shinde and colleagues report on the demographics, sexual behaviours, and sexually transmitted infections including HIV of these sex workers. Of the 75 male sex workers, 24 were men and 51 were transgenders. The mean age of the group was 23.3 (+ 4.9) years. About 15% were married or lived with a permanent partner. Of these individuals, 85% reported sex work as a main source of income and 15% as an additional source. All the individuals reported anal sex (87% anal receptive sex and 13% anal insertive sex). About 13% of male sex workers had never used a condom. The HIV prevalence was 33% (17% in men vs 41% in transgenders,  $P = 0.04$ ). The sexually transmitted infection prevalence was 60% (58% in men vs 61% in transgenders,  $P = 0.8$ ). Syphilis was the most common sexually transmitted infection (28%) in these male sex workers. HIV was associated with being a transgender (41 vs 17%,  $P = 0.04$ ), age > 26 years (57 vs 28%,  $P = 0.04$ ), more than one year of sex work (38 vs 8%,  $P = 0.05$ ), and income  $P = 0.02$ ). These male sex workers have high-risk behaviours, low consistent condom use, and high prevalence of sexually transmitted infections and HIV infections. These groups should be the focus of intensive public health interventions aimed at reduction of risky sexual practices, and prevention and care for both HIV and sexually transmitted infections. **Editors' note: This study did not recruit any male sex workers involved solely in the heterosexual sex trade possibly because such men are less likely to attend this clinic treating sexually transmitted infections (STI). Among the sex worker participants were *kothis*, effeminate men who have sex with men but may also have sex with women, and *hijras*, male-to-female transgendered people who are primarily the receptive partners because of their female gender identity. Overall, only one-third reported always using condoms, with the most common reasons for non-use being non-availability (43%) and refusal of condom use by the partner (20%). Social marginalization of sex workers in India, as elsewhere, hampers the development of effective programmes to help them avoid HIV infection and obtain treatment for STI and HIV. They appear to be considerably more at risk of acquiring HIV infection than do women who sell sexual services and are particularly likely to benefit from improved access to condoms and skills training to enhance condom negotiation.**

Shannon K, Strathdee SA, Shoveller J, Rusch M, Kerr T, Tyndall MW. Structural and Environmental Barriers to Condom Use Negotiation With Clients Among Female Sex Workers: Implications for HIV-Prevention Strategies and Policy. *Am J Public Health*. 2009;99:659-665.

Shannon and colleagues investigated the relationship between environmental-structural factors and condom-use negotiation between female sex workers and clients. They used baseline data from a 2006 Vancouver, British Columbia, community-based cohort of female sex workers, to map the clustering of hot spots for being pressured into unprotected sexual intercourse by a client and assess sexual HIV. The authors then used multivariate logistic modelling to estimate the relationship between environmental-structural factors and being pressured by a client into unprotected intercourse. In multivariate analyses, being pressured to have unprotected sexual intercourse was independently associated with having an individual zoning restriction (odds ratio [OR]=3.39; 95% confidence interval [CI]=1.00, 9.36), working away from main streets because of policing (OR=3.01; 95% CI=1.39, 7.44), borrowing a used crack pipe (OR=2.51; 95% CI=1.06, 2.49), client-perpetrated violence (OR=2.08; 95% CI=1.06, 4.49), and servicing clients in cars or in public spaces (OR=2.00; 95% CI=1.65, 5.73). Given growing global concern surrounding the failings of prohibitive sex-work legislation on sex workers' health, there is urgent need for environmental-structural HIV-prevention efforts that facilitate sex workers' ability to negotiate condom use in safer sex-work environments and criminalize abuse by clients and third parties. **Editors' note: The buying and selling of sexual services has never been illegal in Canada, however it is illegal to communicate in public spaces for the purposes of sexual transaction and the law prohibits 'keeping or transporting a person to a common bawdy-house', thus restricting legal indoor sex work. This study used the risk environment framework as its theoretical base, hypothesising that macro- and meso-level factors outside the individual affect negotiation of individual risk. Trained peer researchers, who were former or current sex workers, interviewed 205 sex workers participating in the Maka Project cohort. They were recruited at sex work strolls at staggered times and spaces along these strolls. The analysis of the effects of enforcement of Canada's prohibitive sex-work policies reveals the need for legal and policy reforms to create safer work environments in which exploitation by clients and third parties is effectively criminalised and condom use is readily and consistently negotiated.**

## 6. *Communications and stigma*

Babalola S, Fatusi A, Anyanti J. Media saturation, communication exposure and HIV stigma in Nigeria. *Soc Sci Med*. 2009;68:1513-1520.

HIV-related stigma constitutes an impediment to public health as it hampers AIDS control efforts in many ways. To address the complex problems of increasing HIV infection rates, widespread misinformation about the infection, and the rising level of HIV-related stigma, the various tiers of government in Nigeria are working with local and international non-governmental organizations to develop and implement strategic communication programmes. This paper assesses the link between these communication efforts and HIV-related stigma using data from a nationally representative household survey. The results show that accepting attitudes towards people living with HIV are more prevalent among men than among women. Exposure to HIV-related communication on the media is associated with increased knowledge about HIV, which is in turn a strong predictor of accepting attitudes. Communication exposure also has a significant and positive association with accepting

attitudes towards people living with HIV. In contrast, community media saturation is not strongly linked with accepting attitudes for either sex. The findings strongly suggest that media-based HIV programs constitute an effective strategy to combat HIV-related stigma and should therefore be intensified in Nigeria. **Editors' note: Community media saturation in this study was defined as the average level of exposure to radio and television of people residing in local areas of residence, and not as actual exposure to HIV-related materials. It is perhaps not surprising therefore that community media saturation made little difference overall on accepting attitudes towards people living with HIV. Radio listening habit was the most significant predictor of HIV campaign exposure, with intensity of exposure in turn varying by sex, education, religion, urban/rural residence, household socio-economic status, and geographic zone of residence. When the messaging is HIV-specific, personal exposure to it is associated with more accepting attitudes for both men and women. However, unmeasured factors operating at community level in Nigeria will have to be addressed to change the community norms that foster stigma towards people living with HIV - simply expanding media-based HIV programming alone is unlikely to have the desired effect.**

### **7. Morbidity and co-morbidity**

Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS*. 2009;23:525-30.

Cryptococcal meningitis is one of the most important HIV-related opportunistic infections, especially in the developing world. In order to help develop global strategies and priorities for prevention and treatment, it is important to estimate the burden of cryptococcal meningitis. Par and colleagues undertook a global burden of disease estimation using published studies. They used the median incidence rate of available studies in a geographic region to estimate the region-specific cryptococcal meningitis incidence; this was multiplied by the 2007 Joint United Nations Programme on HIV/AIDS (UNAIDS) HIV population estimate for each region to estimate cryptococcal meningitis cases. To estimate deaths, the authors assumed a 9% 3-month case-fatality rate among high-income regions, a 55% rate among low-income and middle-income regions, and a 70% rate in sub-Saharan Africa, based on studies published in these areas and expert opinion. Published incidence ranged from 0.04 to 12% per year among persons with HIV. Sub-Saharan Africa had the highest yearly burden estimate (median incidence 3.2%, 720 000 cases; range, 144 000-1.3 million). Median incidence was lowest in Western and Central Europe and Oceania (</=0.1% each). Globally, approximately 957 900 cases (range, 371 700-1 544 000) of cryptococcal meningitis occur each year, resulting in 624 700 deaths (range, 125 000-1 124 900) by 3 months after infection. This study, the first attempt to estimate the global burden of cryptococcal meningitis, finds the number of cases and deaths to be very high, with most occurring in sub-Saharan Africa. Further work is needed to better define the scope of the problem and track the epidemiology of this infection, in order to prioritize prevention, diagnosis, and treatment strategies. **Editors' note: This study estimated that deaths due to cryptococcal meningitis in sub-Saharan Africa may be exceeding those due to tuberculosis. This highlights the substantial disease burden of cryptococcal meningitis and the urgent need to improve diagnostic capacity, expand treatment options, and identify preventive measures. One strategy would promote early detection using the serum cryptococcal antigen test and treatment of asymptomatic or latent cryptococcal infection with**

**fluconazole. Expanding access to antiretroviral treatment is likely helping now to reduce the risk of cryptococcal disease, but disease burden remains very high and serious attention needs to be directed to better public health and clinical management of this disease.**

Beadsworth MB, Cohen D, Ratcliffe L, Jenkins N, Taylor W, Campbell F, Beeching NJ, Azadeh B. Autopsies in HIV: still identifying missed diagnoses. *Int J STD AIDS*. 2009;20:84-6.

This study reviews the deaths and autopsies carried out over 23 years, 1983-2005, in a British Infection Unit in HIV patients. Of 115 HIV patients known to have died, Beadsworth and colleagues obtained data on 93%. Of this 80% were male, median age 38 (25-68) years; 83% were Caucasian; 12% Black African. Major risk factors were men who have sex with men, 52%; heterosexual in Africa, 17%; and injecting drug use, 8%. The commonest diagnosis pre- and post-autopsy diagnosis was pneumonia. Changes in diagnoses in the 38% who underwent autopsy were high (the authors requested autopsy in 50%). Primary diagnosis changed in 70%, and 36% of all opportunistic infections were missed. This included six of nine cytomegalovirus, all tuberculosis, and 75% of Kaposi's sarcoma. Lymphoma was overdiagnosed. Thus, despite excellent resources, the majority of primary diagnoses were wrong, suggesting inadequacy of current diagnostics. To improve these and improve both epidemiological data and future management autopsy should be considered for all deaths. **Editors' note: Although HIV-related mortality has fallen dramatically due to antiretroviral therapy and chemoprophylaxis for opportunistic infections, deaths still occur and we need to better understand what causes them. Autopsy is an important tool for auditing clinical diagnoses, improving diagnostics and management, and enhancing clinical governance in HIV medical practice. This study found errors in the reported primary cause of death in 70% of the deaths occurring in this HIV practice over a 23-year period. Three cases of tuberculosis among the 41 autopsies performed had been completely missed before death. Wherever possible, both physicians and families should request an autopsy in every death of an HIV-positive person in the interests of improved care for those who are living.**

## **8. Reproductive health**

Nattabi B, Li J, Thompson SC, Orach CG, Earnest J. A Systematic Review of Factors Influencing Fertility Desires and Intentions Among People Living with HIV/AIDS: Implications for Policy and Service Delivery. *AIDS Behav*. 2009. DOI 10.1007/s10461-009-9537-y

With availability of antiretroviral treatments, HIV is increasingly recognised as a chronic disease people live with for many years. This paper critically reviews the current literature on fertility desires and reproductive intentions among people living with HIV and critiques the theoretical frameworks and methodologies used. A systematic review was conducted using electronic databases: ISI Web of Knowledge, Science Direct, Proquest, Jstor and CINAHL for articles published between 1990 and 2008. The search terms used were fertility desire, pregnancy, HIV, reproductive decision-making, reproductive intentions, motherhood, fatherhood and parenthood. Twenty-nine studies were reviewed. Fertility desires were influenced by a myriad of demographic, health, stigma-associated and psychosocial factors. Cultural factors were also important, particularly in Sub-Saharan Africa and Asia. Future research that examines fertility desires among people living with HIV should include cultural beliefs and practices in the theoretical framework in order to provide a holistic understanding and to enable development of services that meet the

reproductive needs of people living with HIV. **Editors' note: This interesting systematic review of studies of fertility desires and intentions reveals the importance of mixed methodologies (quantitative and qualitative) to contextualise findings and emphasises the use of theoretical frameworks relevant to cultural context to underpin study design and analyses. In most settings, people living with HIV are uncomfortable talking with health care providers about fertility issues, anticipating or experiencing biased information-giving and negative attitudes. Provision of services within a rights-based framework requires consideration of a risk-reduction approach to minimise vertical and horizontal HIV transmission through nonjudgmental care, treatment, and counselling.**

Cooper D, Moodley J, Zweigenthal V, Bekker LG, Shah I, Myer L. Fertility Intentions and Reproductive Health Care Needs of People Living with HIV in Cape Town, South Africa: Implications for Integrating Reproductive Health and HIV Care Services. *AIDS Behav.* 2009;13:suppl1:38-46.

Tailoring sexual and reproductive health services to meet the needs of people living with the human immuno-deficiency virus (HIV) is a growing concern but there are few insights into these issues where HIV is most prevalent. This cross-sectional study investigated the fertility intentions and associated health care needs of 459 women and men, not sampled as intimate partners of each other, living with HIV in Cape Town, South Africa. An almost equal proportion of women (55%) and men (43%) living with HIV, reported not intending to have children as were open to the possibility of having children (45 and 57%, respectively). Overall, greater intentions to have children were associated with being male, having fewer children, living in an informal settlement and use of antiretroviral therapy. There were important gender differences in the determinants of future childbearing intentions, with being on antiretroviral treatment strongly associated with women's fertility intentions. Gender differences were also apparent in participants' key reasons for wanting children. A minority of participants had discussed their reproductive intentions and related issues with HIV health care providers. There is an urgent need for intervention models to integrate HIV care with sexual and reproduction health counselling and services that account for the diverse reproductive needs of these populations. **Editors' note: This 2006 exploratory survey of fertility intentions among people living with HIV attending two public sector health centres in a high HIV prevalence residential area of Cape Town found that only 19% of women and 6% of men had consulted a doctor, nurse, or counsellor in HIV care about fertility intentions. Among women in HIV care, 11% had become pregnant since their HIV diagnosis, all unintentionally. Among women on antiretroviral treatment, 9% had become pregnant since starting treatment, with 30% of these pregnancies reportedly unintentional. On-site integration of sexual and reproductive health services into HIV care settings is urgently required in order to create space for discussions with women and men about their fertility intentions; to provide easy access to contraceptive measures for those who desire to postpone, prevent or discontinue pregnancies; and to provide timely antiretroviral prophylaxis to prevent mother-to-child transmission.**

## **9. Vaccine vectors**

Lemiale F, Korokhov N. Lentiviral vectors for HIV disease prevention and treatment. *Vaccine.* 2009; 27:3443-3449.

HIV has posed major challenges to the scientific community, both in terms of treatment and prevention. Current drug regimens, while efficacious, are expensive, inaccessible to major

parts of the world, induce major side effects, and cannot prevent escape mutants due to lack of compliance and drug fatigue. In the vaccine field, recent setbacks related to the interruption and cancellation of major advanced clinical trials using adenoviral vectors have highlighted the need for new and innovative strategies. Unique features of HIV-based lentiviral vectors (LVs) and the current progress in the LV-based platform development make them an attractive alternative for the further LV-based HIV vaccine development. In preclinical studies, they have demonstrated a high degree of immunogenicity, while overcoming pitfalls faced by other viral vectors. These findings, combined with recent progress in large scale lentiviral vectors production/purification, make this strategy worth considering for further vaccine development. **Editors' note: In making the case for further study of lentiviral vectors, this article provides a description of the evolution of HIV vaccine strategies. These aim to overcome the challenges of HIV-1 sequence diversity, latency, high rates of mutation and recombination, and infection by HIV of critical immune cells. Among the current approaches are strategies using protein-based formulations to induce neutralising antibodies and vector systems to induce cellular immunity - we will likely need both for an effective HIV vaccine.**

Wang L, Cheng C, Ko SY, Kong WP, Kanekiyo M, Einfeld D, Schwartz RM, King CR, Gall JG, Nabel GJ. Delivery of adenovirus HIV vaccine vectors to the intestine induces enhanced mucosal cellular immunity. *J Virol*. 2009;83:7166-75.

Effective vaccines for human immunodeficiency virus-1 (HIV-1) will likely need to stimulate protective immunity in the intestinal mucosa, where HIV-1 infection causes severe CD4(+) T cell depletion. While replication-competent adenoviral vectors (rAd) can stimulate Ad-specific mucosal immunity after replication, oral delivery of replication-defective rAd vectors encoding specific immunogens has proven challenging. In this study, Wang and colleagues have systematically identified barriers to effective gut delivery of rAd vectors and identify sites and strategies to induce potent cellular and humoral immunity. Vector-mediated gene transfer by rAd5 was susceptible to low pH buffer, gastric and pancreatic proteases, and extracellular mucins. Using ex vivo organ explants, they found that transduction with rAd5 was highest in the ileum and colon compared to other intestinal segments. Transgene expression was 100-fold higher after direct surgical introduction into the ileum than observed with oral gavage, with rAd5 showing greater potency than rAd35 or rAd41 vectors. A single immunization of rAd5 encoding HIV-1 gp140B to the ileum stimulated potent CD8(+) T cell responses in the intestinal and systemic compartments, and these responses were further enhanced by intramuscular rAd5 boosting. These studies suggest that induction of primary immune responses by rAd5 gut immunization elicits potent antigen-specific mucosal responses after subsequent systemic boosting. **Editors' note: This study is one of a series of studies aimed at determining whether different adenovirus vectors with alternative routes of administration can enhance mucosal immunity. Because the gastrointestinal tract is the predominant site of CD4 T-cell loss during the first weeks of HIV infection, these researchers hypothesized that targeted delivery of vaccines to the gut could stimulate mucosal responses that would inhibit uncontrolled viral replication and protect gut-associated lymphoid tissue (GALT). Immune responses induced by a single injection into the small bowel of a recombinant adenovirus encoding gp140B, followed by an intramuscular boost, produced strong cellular immune responses in mice. Whether this will have clinical utility in the future is anyone's guess (a small bowel**

injection to prevent HIV seems quite a stretch), but it is a good model for learning more about how mucosal immune responses contribute to protection against HIV.

#### 10. *Prevention of mother-to-child transmission*

Deschamps MM, Noel F, Bonhomme J, Dévieux JG, Saint-Jean G, Zhu Y, Wright P, Pape JW, Malow RM. Prevention of mother-to-child transmission of HIV in Haiti. *Rev Panam Salud Publica*. 2009;25:24-30.

Deschamps and colleagues set out to describe the effectiveness of a program designed to reduce the rate of mother-to-child transmission of HIV at the primary HIV testing and treatment center in Haiti between 1999 and 2004. All pregnant, HIV-positive women who attended the major HIV testing and treatment clinic in Port-au-Prince, Haiti, between March 1999 and December 2004 were asked to participate in a mother-to-child transmission prevention program. Of the 650 women who participated, 73.3% received zidovudine (AZT), 2.9% received nevirapine (NVP), and 10.1% received triple-drug therapy when it became available in 2003 and if clinical/laboratory indications were met. Approximately 13.8% received no antiretroviral medication. All participants received cotrimoxazole prophylaxis and infant formula for their children. Kaplan-Meier survival analysis and the log rank test were used to evaluate program impact on child survival. Complete data were available for 348 mother-infant pairs who completed the program to prevent mother-to-child transmission of HIV. The rate of mother-to-child transmission in the study was 9.2% (95% CI:6.14-12.24), in contrast to the historical mother-to-child transmission rate of 27% in Haiti. HIV-positive infants were less likely to survive than HIV-negative infants at 18 months of follow-up ( $\chi^2 = 19.06$ ,  $P < .001$ , log rank test). Infant survival improved with early paediatric diagnosis and antiretroviral treatment. The mother-to-child transmission prevention program described proved to be feasible and effective in reducing vertical HIV transmission in Haiti. The authors emphasize the need to expand testing, extend services to rural areas, and implement early HIV diagnosis to reduce infant mortality. **Editors' note: Over the period from 1999 to 2004 the annual number of women who agreed to undergo HIV testing at the GHESKIO clinic more than doubled and the number of HIV-positive women who enrolled in the prevention of mother-to-child transmission (PMTCT) programme quadrupled. Overall 43,173 women at higher risk of HIV exposure were tested (18.3% were HIV-positive) and 5270 were pregnant (12.3% HIV-positive). Of the 650 HIV-positive pregnant women, 28.7% did not participate in the PMTCT programme, primarily because they returned to rural areas, and only 14% were able to bring their partners in for HIV testing. After delivery, 73.9% of the women were using family planning services at 18-month follow-up compared to national uptake data of 23%. Despite persistent instability and violence in Haiti, this programme in Port-au-Prince has successfully reduced HIV transmission to infants to one-third of the historical rate. With a 2007 adult (15-49 years) HIV prevalence of 2.2% (1.9-2.5), in a league with the Bahamas, Guyana, Suriname, and Belize in the Americas, Haiti clearly needs a nationwide programme integrating family planning, voluntary counselling and testing, and HIV treatment services with good referral links between centres.**

Cailhol J, Jourdain G, Coeur SL, Traisathit P, Boonrod K, Prommas S, Putiyanun C, Kanjanasing A, Lallemand M; for the Perinatal HIV Prevention Trial Group. Association of Low CD4 Cell Count and Intrauterine Growth Retardation in Thailand. *J Acquir Immune Defic Syndr*. 2009; 50:409-413.

Each year, intrauterine growth retardation affects 20-30 million neonates worldwide, mostly in resource-limited settings. Increased perinatal and infant mortality has been associated with intrauterine growth retardation. Some studies have suggested that HIV infection could increase the risk of intrauterine growth retardation. To confirm this hypothesis, Cailhol and colleagues examined the association between HIV-related factors and the risk of intrauterine growth retardation in Thailand. Data from a cohort of 1436 HIV-infected pregnant women enrolled in the « Perinatal HIV Prevention Trial-1 », a clinical trial conducted from 1997 to 1999 in Thailand, were analyzed using a logistic regression, adjusting for risk factors usually associated with intrauterine growth retardation. The rate of intrauterine growth retardation was 7.6%. Adjusting for a short maternal height, low body mass index, small weight gain during pregnancy, and infant female sex, a low maternal CD4 percentage was independently associated with intrauterine growth retardation (odds ratio 0.96, per 1% increment, 95% confidence interval 0.93 to 0.99, P = 0.03). The current World Health Organization recommendation to initiate combination antiretroviral therapy for immunocompromised women as early as possible during pregnancy for their own health and for the prevention of HIV mother-to-child transmission is likely to also decrease the incidence of intrauterine growth retardation. Encouraging immunocompromised HIV-infected women who plan to become pregnant to wait until immune restoration has been achieved may help to reduce the risk of intrauterine growth retardation. **Editors' note: Intrauterine growth retardation (IUGR) is the second cause of perinatal mortality after prematurity. It is associated with higher susceptibility to various conditions in the neonatal period as well as with diseases in adulthood such as diabetes, obesity, and hypertension. This Thai study used the stringent definition of IUGR of 'birth weight below the 10<sup>th</sup> percentile of weight for the corresponding gestational age', rather than the low birth weight cut-off of 2500 g which can indicate prematurity. Also it used CD4 percentage which is less variable than absolute CD4 count. The finding that CD4 percentage below the median contributed 28% of the risk of IUGR in this population gives added support to the recommendation to initiate antiretroviral treatment (as opposed to antiretroviral prophylaxis) in pregnancy for women with low CD4 counts.**

That was *HIV this week*, signing off.

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