

HIV This Week: what scientific journals said

Welcome to the 65th issue of *HIV This Week*! In this issue, we cover **policy and law** (ten good reasons against criminalisation of HIV; high time to walk the talk and invoke the law on condom access for youth in South Africa), **stem cells** (the famous German case appears in the peer reviewed scientific literature; umbilical cord blood stem cells selected for CCR5 Delta32/Delta32 deletions could hold promise for HIV treatment), **sexual transmission** (a meta-analysis suggests but does not explain why low-income countries might have higher heterosexual transmission probabilities), **prevention trial conduct** (South African research ethics committee members care more about consent than about the consent form compared to their US counterparts), **adherence** (social capital - we need more of it everywhere, and not just for HIV treatment adherence and not just in Africa), **stigma** (how treatment can increase stigma in rural Tanzania; the need to build social cohesion, trust, and community networks to support HIV testing and disclosure in rural KwaZulu-Natal), **epidemiology** (does differential population HIV susceptibility help explain recent HIV prevalence declines in Africa?; risk factors for HIV in Andhra Pradesh: what's male circumcision got to do with it?), **microbicides** (an excellent review to cut out and keep; drawing lessons about adherence to gel from the negative Carraguard trial in South Africa), **male circumcision** (circumcision helps protect heterosexual African American men exposed to HIV; uncircumcised US men who have sex with men would get circumcised as adults if it would reduce their HIV risk), **paediatric diagnosis** (pending illusive point-of-care testing, dried blood spots shipped for rapid real-time PCR diagnosis are the next best thing for diagnosing rural HIV-exposed infants; when best to try to diagnose breastfed infants in order to start timely treatment; lessons from Zimbabwe: what to do if there is only antibody testing), **universal access** (marrying science and optimized HIV care in resource-limited settings; feasibility of traditional birth attendant integration in prevention of mother-to-child transmission services in rural Africa), **cost-effectiveness** (pre-exposure prophylaxis: real efficacy data are needed for useful analyses), **prevention of mother-to-child transmission** (mitochondrial toxicity and preventing mother-to-child transmission: what are the trade-offs?), and **country responses: government and university collaborations** (Lesotho and Boston U share their mutual lessons learned).

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you can find a wealth of information on the HIV epidemic and responses to it at www.unaids.org

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1. Policy and law

Cameron E, Burris S, Clayton M. HIV is a virus, not a crime: ten reasons against criminal statutes and criminal prosecutions. *J Int AIDS Soc.* 2008;11(1):7. [Epub ahead of print]

The widespread phenomenon of enacting HIV-specific laws to criminally punish transmission of, exposure to, or non-disclosure of HIV, is counter-active to good public health conceptions and repugnant to elementary human rights principles. The authors provide ten reasons why criminal laws and criminal prosecutions are bad strategy in the epidemic. **Editors' note: HIV is a virus not a crime and criminalisation of HIV is hostile to both HIV prevention and treatment. Knowing one's HIV status and setting out deliberately to infect another person and achieving this aim demonstrates criminal intent warranting prosecution. However, there is no public health justification for invoking criminal law sanctions against those who unknowingly and unintentionally transmit HIV or expose others to it. Such criminalisation discourages HIV testing and counselling, the pathway to treatment access and HIV status-specific prevention; reinforces stigma, enhances fear, and isolates people living with HIV; and undercuts efforts to address the epidemic.**

Han J, Bennish ML. Condom access in South African schools: law, policy, and practice. *PLoS Med.* 2009;6(1):e6.

South Africa's recently adopted Children's Act provides children the right to access reproductive health services as a way of addressing the HIV pandemic, but there remains confusion about how socially divisive rights provided for by the Act, such as condom access for youth, will be achieved. The Children's Act, together with South African government policies, allows individual schools to decide whether to distribute condoms, but most school staff are unaware of South African policy and regulations governing condom provision in schools. Because of confusing and contradictory government policies and public pronouncements regarding provision of condoms in public schools, few schools have undertaken to provide condoms, leaving students, especially in rural areas, with few options for obtaining them. US President's Emergency Plan for AIDS Relief regulations potentially conflict with South African law by prohibiting US President's Emergency Plan for AIDS Relief-funded organizations from distributing condoms in schools or providing condom information to youth aged 14 and under. The current South African government's policy of leaving the decision of whether to distribute condoms in schools to the School Governing Body of individual schools, rather than enacting a clear national policy, is unlikely to be an effective public health strategy for improving access to condoms for the population of youths at high risk for HIV. **Editors' note: South Africa permits 12 year olds to consent on their own to HIV testing but walking the talk on condom access for youth seems a challenge. The Children's Act grants children age 12 and older access to condoms but adults, both domestic and foreign, are blocking implementation of this legally sanctioned right. Schools are good venues for youth, teachers, parents, community leaders, and health workers to come together to discuss constructive steps forward in the context of a relentless epidemic and a seeming policy vacuum.**

2. Stem cells

Hütter G, Nowak D, Mossner M, Ganepola S, Müssig A, Allers K, Schneider T, Hofmann J, Kücherer C, Blau O, Blau IW, Hofmann WK, Thiel E. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N Engl J Med*. 2009;360(7):692-8.

Infection with the human immunodeficiency virus type 1 (HIV-1) requires the presence of a CD4 receptor and a chemokine receptor, principally chemokine receptor 5 (CCR5). Homozygosity for a 32-bp deletion in the CCR5 allele provides resistance against HIV-1 acquisition. Hütter and colleagues transplanted stem cells from a donor who was homozygous for CCR5 delta32 in a patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. This outcome demonstrates the critical role CCR5 plays in maintaining HIV-1 infection. **Editors' note: After 20 months, this patient's CD4+ counts are in the normal range; HIV-1 is not detectable in blood, bone marrow, or rectal mucosa; and the disappearance of the effector T-cells that normally fight HIV suggests that HIV is not around to provoke them. The patient could still be harbouring a CXCR4 type of HIV; many people die from bone marrow transplantation procedures, and people lacking CCR5 may be more susceptible to serious effects from certain infections. Nonetheless, this case will continue to be followed with interest and will no doubt open the door to further innovations in HIV treatment.**

Behringer RR, Gonzalez G, Shpall EJ, Gathe J. Cord blood stem cell therapy for acquired immune deficiency syndrome. *Stem Cells Dev*. 2008. [Epub ahead of print]

Cord blood stem cell transplantation is routinely used to treat hematopoietic diseases. Individuals who are homozygous for the Delta32 polymorphism of the CCR5 locus, encoding a co-receptor for HIV-1, are normal and resistant to HIV infection. Here Behringer and colleagues suggest that public cord blood repositories are likely to contain CCR5 homozygous units that could be used as a therapy for HIV infected individuals. **Editors' note: Cord blood stem cells, collected non-invasively from the placenta and umbilical cord after separation from a newborn, are less mature and would require less matching between donor and recipient than is the case for a bone marrow transplant. Homozygosity of the CCR5 delta 32 allele (meaning both chromosomes have the same 32 base pair deletion) occurs in 1 to 3% of current cord bank specimens in western populations that have high allele frequencies. The idea of cord stem cells for HIV treatment has yet to be explored but may have some merit.**

3. Sexual transmission

Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, Alary M. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis*. 2009;9(2):118-29.

Boily and colleagues did a systematic review and meta-analysis of observational studies of the risk of HIV-1 transmission per heterosexual contact. 43 publications comprising 25 different study populations were identified. Pooled female-to-male (0.04% per act [95% CI 0.01-0.14]) and male-to-female (0.08% per act [95% CI 0.06-0.11]) transmission estimates in high-income countries indicated a low risk of infection in the absence of antiretrovirals. Low-income country female-to-male (0.38% per act [95% CI 0.13-1.10]) and male-to-female (0.30% per act [95% CI 0.14-0.63]) estimates in the absence of commercial sex exposure

were higher. In meta-regression analysis, the infectivity across estimates in the absence of commercial sex exposure was significantly associated with sex, setting, the interaction between setting and sex, and antenatal HIV prevalence. The pooled receptive anal intercourse estimate was much higher (1.7% per act [95% CI 0.3-8.9]). Estimates for the early and late phases of HIV infection were 9.2 (95% CI 4.5-18.8) and 7.3 (95% CI 4.5-11.9) times larger, respectively, than for the asymptomatic phase. After adjusting for commercial sex exposure, presence or history of genital ulcers in either couple member increased per-act infectivity 5.3 (95% CI 1.4-19.5) times versus no sexually transmitted infection. Study estimates among non-circumcised men were at least twice those among circumcised men. Low-income country estimates were more heterogeneous than high-income country estimates, which indicates poorer study quality, greater heterogeneity of risk factors, or under-reporting of high-risk behaviour. Efforts are needed to better understand these differences and to quantify infectivity in low-income countries. **Editors' note: Transmission probabilities depend on the infectiousness of the HIV-infected partner and the susceptibility of the uninfected partner, both of which depend on behavioural, genetic, and immunological risk factors affecting the host and the virus. The higher transmission probabilities for low-income than for high-income countries derived here may reflect differential viral subtypes, more sexually transmitted co-infections, mutation of chemokine receptor genes, interactions with other infectious diseases, misreporting of risk behaviour, or other explanations. Adequately powered, carefully planned discordant couple studies would help determine per act infectivity and assist in the design of appropriate prevention strategies.**

4. Prevention trial conduct

Klitzman R. Views of the process and content of ethical reviews of HIV vaccine trials among members of US Institutional Review Boards and South African Research Ethics Committees. *Dev World Bioeth.* 2008;8(3):207-18.

Given the ethical controversies concerning HIV vaccine trials, Klitzman aimed to understand through an exploratory study how members of institutional review boards in the United States and research ethics committees in South Africa view issues concerning the process and content of reviews of these studies. The author mailed packets of 20 questionnaires to 12 United States institutional review board chairs and administrators and seven research ethics committee chairs to distribute to their members. Klitzman received 113 questionnaires (76 from the United States and 37 from South Africa). In both countries, members tended to be white males with advanced academic degrees. Compared to the United States, South African members called for 'major changes' in HIV vaccine trial protocols more frequently (p = 0.004), and were less likely to think that HIV vaccine trial participants understood risks and benefits (p = 0.033) or informed consent forms (p = 0.000). In both countries, members were divided on several critical issues (e.g. the minimum standard for treatment for HIV vaccine trial participants who became infected during the HIV vaccine trial), but agreed that they needed more training. Of the South African respondents, 40% reported that they were 'self-taught' in ethics. This study, the first we know of to offer quantitative data comparing US vs. non-US institutional review boards/research ethics committees, thus suggests key similarities and differences (e.g. compared to South African respondents, United States respondents appeared to overestimate participants' understanding of informed consent), along with needs for education. These initial exploratory data in this area have important implications for institutional review boards, research ethics

committees, policy-makers and scholars concerning future practice, training, policy, and investigations in research ethics, and prevention and treatment of HIV and other diseases in the developing world and elsewhere. **Editors' note: This study did not take into account the 2007 UNAIDS/WHO Ethical considerations in biomedical HIV prevention trials document which contains explicit guidance on treatment for trial participants who acquire HIV infection during the course of a trial. Nonetheless, the comparative findings reported here suggest that lack of ethnic diversity in committee membership is a problem for institutional review boards/ethics committees in both the South African and US contexts. South African research ethics committee members may have had more field experience - they had better awareness of how trial participants might or might not comprehend key issues. This supports the idea that local institutional review boards/ethics committees are best placed to assess whether procedures and practices are likely to ensure that consent is truly informed.**

5. Adherence

Ware NC, Idoko J, Kaaya S, Biraro IA, Wyatt MA, Agbaji O, Chalamilla G, Bangsberg DR. Explaining adherence success in sub-Saharan Africa: an ethnographic study. *PLoS Med.* 2009;6(1):e11.

Individuals living with HIV in sub-Saharan Africa generally take more than 90% of prescribed doses of antiretroviral therapy. This number exceeds the levels of adherence observed in North America and dispels early scale-up concerns that adherence would be inadequate in settings of extreme poverty. This paper offers an explanation and theoretical model of antiretroviral therapy adherence success based on the results of an ethnographic study in three sub-Saharan African countries. Determinants of antiretroviral therapy adherence for HIV-infected persons in sub-Saharan Africa were examined with ethnographic research methods. 414 in-person interviews were carried out with 252 persons taking antiretroviral therapy, their treatment partners, and health care professionals at HIV treatment sites in Jos, Nigeria; Dar es Salaam, Tanzania; and Mbarara, Uganda. 136 field observations of clinic activities were also conducted. Data were examined using category construction and interpretive approaches to analysis. Findings indicate that individuals taking antiretroviral therapy routinely overcome economic obstacles to antiretroviral therapy adherence through a number of deliberate strategies aimed at prioritizing adherence: borrowing and "begging" transport funds, making "impossible choices" to allocate resources in favour of treatment, and "doing without". Prioritization of adherence is accomplished through resources and help made available by treatment partners, other family members and friends, and health care providers. Helpers expect adherence and make their expectations known, creating a responsibility on the part of patients to adhere. Patients adhere to promote good will on the part of helpers, thereby ensuring help will be available when future needs arise. Adherence success in sub-Saharan Africa can be explained as a means of fulfilling social responsibilities and thus preserving social capital in essential relationships. **Editors' note: Social capital concerns trust, cooperation, reciprocity, and sociability grounded in networks of social relationships. It explains treatment adherence in some societies, as this qualitative study has found, as well as the reason that the threat of stigma leading to social isolation undermines relationships essential to survival. It has been noted that social capital, unlike other types of capital, increases with use, which is good, but social capital does not address the fundamental problem of poverty. Affordable transportation, nutritious food, and clean water can help people on**

antiretroviral treatment living in extreme poverty adhere to treatment, fulfil their social responsibilities, and preserve the relationships they rely on to survive.

6. Stigma

Roura M, Urassa M, Busza J, Mbata D, Wringe A, Zaba B. Scaling up stigma? The effects of antiretroviral roll-out on stigma and HIV testing. Early evidence from rural Tanzania. *Sex Transm Infect.* 2008. [Epub ahead of print]

This study aimed to investigate the interplay between antiretroviral therapy scale-up, different types of stigma, and voluntary counselling and testing uptake two years after the introduction of free antiretroviral therapy in a rural ward of Tanzania. Qualitative study using in-depth interviews and group activities with a purposive sample of 91 community leaders, 77 antiretroviral therapy clients and 16 health providers. Data were analysed for recurrent themes using NVIVO-7 software. The complex interplay between antiretroviral therapy, stigma, and voluntary counselling and testing in this setting is characterised by two powerful but opposing dynamics. The availability of effective treatment has transformed HIV into a manageable condition which is contributing to a reduction of self-stigma and is stimulating uptake of voluntary counselling and testing. However, this is counter-balanced by the persistence of blaming attitudes and emergence of new sources of stigma associated with antiretroviral therapy provision. The general perception among community leaders was that as antiretroviral therapy users regained health they increasingly engaged in sexual relations and «spread the disease». Fears were exacerbated because they were perceived to be very mobile and difficult to identify physically. Some leaders suggested giving antiretroviral therapy recipients drugs «for impotence», marking them «with a sign», and putting them «in isolation camps». In this context, traditional beliefs about disease aetiology provided a less stigmatised explanation for HIV symptoms contributing to a situation of collective denial. Where anticipated stigma prevails, provision of antiretroviral drugs alone is unlikely to have sufficient impact on voluntary counselling and testing uptake. Achieving widespread public health benefits of antiretroviral therapy roll-out requires community-level interventions to ensure local acceptability of antiretroviral drugs. **Editors' note: Stigma may be internalized (self-stigma), anticipated (stigma people expect from others), secondary (affecting those related to the infected person) or enacted stigma (discrimination). Stigma related to inability of ill people living with HIV to conduct productive activities and care for themselves ('drain of resources') may be reduced by the health enhancing effects of antiretroviral treatment as people regain weight and energy. However, without social analysis, community engagement, and careful planning, scaling up antiretroviral treatment can lead to new sources of treatment-associated stigma that ostracizes people on treatment and dissuades others from learning their HIV serostatus.**

Abdool Karim Q, Meyeer-Weitz A, Mboyi L, Carrara H, Mahlase G, Frohlich JA, & Abdool Karim SS. The influence of AIDS stigma and discrimination and social cohesion on HIV testing and willingness to disclose HIV in rural KwaZulu-Natal. *South Africa Global Public Health.* 2008; 3(4):351-365.

This study aims to understand the influence of AIDS stigma and discrimination, and social cohesion to HIV testing, and willingness to disclose an HIV status. A cross-sectional, interviewer administered survey (N=594) was conducted. Independent sample t-tests explored the mean differences between sex and age groups on stigma, discrimination, and

social cohesion measurement. Logistic regression models were fitted with the above independent variables, and the binominal dependent variables: having had a test, willingness to have a test and disclose a positive status. The mean age of participants was 25.3 years and 60% were women. Only 28% had an HIV test, 63% were willing to have a test, and 82% reported a willingness to disclose an HIV status. High levels of stigma and discrimination were anticipated from the community, less so from their partners, and very little from families. Low levels of social distance exist towards people with HIV, membership to social networks seems limited, and inadequate social support for people with HIV was reported. The analysis indicates that AIDS stigma and discrimination, and inadequate social cohesion, limit access to voluntary counselling and testing, inhibit disclosure, and are, thus, barriers to care, support and prevention. Interventions need to extend the focus on information and education to strengthen social capital within a participatory and sustainable development framework.

Editors' note: If they were to test HIV-positive, over 85% of respondents in this rural household survey anticipated support and compassion from their families but thought the community would gossip about them (86%), assume they have been unfaithful (84%), judge them as promiscuous (83%) or not pray for them (63%). Strong family cohesion could be a platform from which to extend and strengthen other forms of social capital, such as social cohesion, trust, and networks in the community to facilitate social support for people living with HIV and confront AIDS stigma. Without broad-based community mobilisation to address stigma and discrimination in this and similar settings, HIV testing uptake will remain low and uptake of antiretroviral treatment limited, despite beliefs that families will care and love their members who are found to be HIV-positive.

7. Epidemiology

Nagelkerke N, de Vlas SJ, Jha P, Luo M, Plummer FA, Kaul R. Heterogeneity in host HIV susceptibility as a potential contributor to recent HIV prevalence declines in Africa. *AIDS*. 2009;23(1):125-30.

HIV prevalence has recently declined in several African countries, and prior to this the risk of HIV acquisition per unprotected sex contact also declined in Kenyan sex workers. Nagelkerke and colleagues hypothesized that heterogeneity in HIV host susceptibility might underpin both of these observations. A compartmental mathematical model was used to explore the potential impact of heterogeneity in susceptibility to HIV infection on epidemic behaviour, in the absence of other causative mechanisms. Studies indicated that a substantial heterogeneity in susceptibility to HIV infection may lead to an epidemic that peaks and then declines due to a depletion of the most susceptible individuals, even without changes in sexual behaviour. This effect was most notable in high-risk groups such as female sex workers and was consistent with empirical data. Declines in HIV prevalence may have other causes in addition to behaviour change, including heterogeneity in host HIV susceptibility. There is a need to further study this heterogeneity and its correlates, particularly as it confounds the ability to attribute HIV epidemic shifts to specific interventions, including behaviour change.

Editors' note: Although there is compelling evidence that the HIV prevalence declines observed in many parts of Africa were likely caused by changes in risk behaviour, this model predicts that unevenly distributed susceptibility may have played a role. Genetic, immune, and infectious correlates of altered susceptibility mean that early HIV acquisition by more susceptible hosts may leave behind more resistant populations with reduced HIV incidence. Despite these

underlying epidemic currents, HIV prevalence levels can remain high and each day the millions of young people who become sexually active join the ranks of the susceptible, underscoring the need for intensified combination prevention.

Dandona L, Dandona R, Kumar GA, Reddy GB, Ameer MA, Ahmed GM, Ramgopal SP, Akbar M, Sudha T, Lakshmi V. Risk factors associated with HIV in a population-based study in Andhra Pradesh state of India. *Int J Epidemiol.* 2008;37(6):1274-86. Epub 2008.

Population-based data on risk factors associated with HIV are not readily available from India. This understanding, and an estimate of the impact of addressing behavioural factors on reducing HIV, would be useful. Dandona and colleagues interviewed a population-based sample of 12,617 persons 15-49 years old from 66 rural and urban clusters in Guntur district in the south Indian state of Andhra Pradesh and tested their dried blood spots for HIV. They used multiple logistic regression to assess the association of risk factors with HIV, and calculated population impact numbers for HIV reduction if behavioural factors were addressed. Among men, there was significant association between HIV and history of sex with men, blood transfusion, having ever visited sex worker or multiple lifetime women sex partners, consuming alcohol before sex, recreational drug use, male non-circumcision, and tattooing (odds ratios 5.74-1.97, $P < 0.03$, $R(2) = 0.11$). Among women, the only identified behavioural factor associated with HIV was multiple lifetime men sex partners ($P = 0.001$, $R(2) = 0.10$). Taking into account the relative risk and prevalence of risk factors, the highest impact on reducing the HIV number per unit population was for male circumcision. Among the identified factors, male circumcision was estimated to have the highest relative impact on reducing HIV per unit population, but the feasibility of this intervention in India needs further investigation. The low explanatory power in the regression models of the usually considered risk factors for HIV suggests that better understanding of HIV dynamics at the population level in India is needed. **Editors' note: In this analysis, behavioural risk variables could explain only a small fraction of the variability of prevalent HIV in the Andhra Pradesh population - 11% for men and 10% for women. This may be because there are associations other than recognized risk factors that were not explored or perhaps there was incomplete reporting by respondents about sensitive risk behaviour (8.8% of women and 43.4% of men reported having had sex with more than one person in their life). That male circumcision in urban men in India would have the biggest impact in reducing HIV prevalence provides food for thought in this country where male circumcision is associated with religious identity. Acceptability studies, community conversations, and situational analyses would be needed to assess the relevance of male circumcision for HIV prevention, along with prevention of human papilloma virus infection and genital ulcer disease in India.**

8. Microbicides

Cutler B, Justman J. Vaginal microbicides and the prevention of HIV transmission. *Lancet Infect Dis.* 2008;8(11):685-97.

Worldwide, nearly half of all individuals living with HIV are now women, who acquire the virus largely by heterosexual exposure. With an HIV vaccine likely to be years away, topical microbicide formulations applied vaginally or rectally are being investigated as another strategy for HIV prevention. A review of preclinical and clinical research on the development of microbicides formulated to prevent vaginal HIV transmission yielded 118 studies: 73 preclinical and 45 clinical. Preclinical research included in-vitro assays and cervical explant

models, as well as animal models. Clinical research included phase I and II/IIb safety studies, and phase III efficacy studies. Whereas most phase I and phase II clinical trials have found microbicide compounds to be safe and well tolerated, phase III trials completed to date have not demonstrated efficacy in preventing HIV transmission. Topical microbicides are grouped into five classes of agents, based on where they disrupt the pathway of sexual transmission of HIV. These classes include surfactants/membrane disruptors, vaginal milieu protectors, viral entry inhibitors, reverse transcriptase inhibitors, and a fifth group whose mechanism is unknown. The trajectory of microbicide development has been toward agents that block more specific virus-host cell interactions. Microbicide clinical trials face scientifically and ethically complex issues, such as the choice of placebo gel, the potential for viral resistance, and the inclusion of HIV-infected participants. Assessment of combination agents will most likely advance this field of research. **Editors' note: This excellent review was conducted before the results of the HPTN035 PRO 2000 trial were announced in February. This phase II/IIb safety/test of concept trial found a statistically non-significant but encouraging 30% protection for women in the experimental arm using the sulfonated polymer naphthalene sulfonate gel (0.5% PRO 2000). Sub-analyses revealed a strong dose-response relationship with the best protection seen in high gel, low condom users. Through their negative charge, anionic polymers interact with HIV's envelope proteins, interfering with the attachment of HIV to CD4+ cells. A pivotal phase III efficacy trial, the UK Microbicide Development Programme's MDP-301 trial of 0.5% PRO 2000 involving 9673 women is expected to report findings in late 2009/early 2010 that may confirm or contradict the HPTN035 results. These are interesting days in the microbicide world.**

Skoler-Karpoff S, Ramjee G, Ahmed K, Altini L, Plagianos MG, Friedland B, Govender S, De Kock A, Cassim N, Palanee T, Dozier G, Maguire R, Lahteenmaki P. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372(9654):1977-87.

Female-initiated HIV-prevention options, such as microbicides, are urgently needed. Skoler-Karpoff and colleagues assessed Carraguard, a carrageenan-based compound developed by the Population Council, for its efficacy and long-term safety in prevention of HIV infection in women. The authors undertook a randomised, placebo-controlled, double-blind trial in three South African sites in sexually-active, HIV-negative women, aged 16 years and older. 6202 participants, who were randomly assigned by a block randomisation scheme to Carraguard (n=3103) or placebo (methylcellulose [n=3099]), were instructed to use one applicator of gel plus a condom during each vaginal sex act. Participants were followed up for up to 2 years. Visits every 3 months included testing for HIV presence and pregnancy, pelvic examinations, risk reduction counselling, and treatment for curable sexually transmitted infections and symptomatic vaginal infections. The primary outcome was time to HIV seroconversion. Analysis was in the efficacy population (a subset of the intention-to-treat population, excluding participants for whom efficacy could not be assessed). This study is registered with ClinicalTrials.gov, number NCT00213083. For the primary outcome (time to HIV seroconversion) the researchers analyzed 3011 women in the Carraguard group and 2994 in the placebo group. HIV incidence was 3.3 per 100 woman-years (95% CI 2.8-3.9) in the Carraguard group (134 events) and 3.8 per 100 woman-years (95% CI 3.2-4.4) in the placebo group (151 events), with no significant difference in the distribution of time to seroconversion (p=0.30). The covariate-adjusted hazard ratio was 0.87 (95% CI 0.69-1.09).

Rates of self-reported gel use (96.2% Carraguard, 95.9% placebo) and condom use (64.1% in both groups) at last sex acts were similar in both groups. On the basis of applicator testing, however, gel was estimated to have been used in only 42.1% of sex acts, on average (41.1% Carraguard, 43.1% placebo). 1420 (23%) women in the intention-to-treat population had adverse events (713 Carraguard, 707 placebo), and 95 (2%) women had adverse events that were related to gel use (48 Carraguard, 47 placebo). Serious adverse events occurred in 72 (2%) women in the Carraguard group and 78 (3%) in the placebo group, only one of which was considered possibly related to gel use (placebo group). This study did not show Carraguard's efficacy in prevention of vaginal transmission of HIV. No safety concerns were recorded.

Editors' note: Carraguard is a non-contraceptive odourless gel containing the sulfated negatively-charged polysaccharide carrageenan derived from seaweed, which had shown promise in vitro and in mouse models, Although the results of this trial were disappointing - Carraguard is safe but not protective at the 33% target level of the trial - it was a well-designed, well-run efficacy trial from which we can learn. The contrast between high rates of self-reported gel use and the low proportion of covered sex acts (based on the applicator tests) underscore the importance of improved data collection methods for measuring adherence. If the gel use indicator of 42% is close to reality, product efficacy would have had to be at least 70% to detect an effect. Coitally-dependent products require high adherence for protection - we know this from the condom world. Lower than expected adherence to gel use in this trial made it more likely that a protective effect would not be found.

9. Male circumcision

Warner L, Ghanem KG, Newman DR, Macaluso M, Sullivan PS, Erbelding EJ. Male Circumcision and Risk of HIV Infection among Heterosexual African American Men Attending Baltimore Sexually Transmitted Disease Clinics. *J Infect Dis.* 2009;199(1):59-65.

Male circumcision has received international attention as an intervention for reducing HIV infection among high-risk heterosexual men; however, few US studies have evaluated its association with the risk of HIV infection. Warner and colleagues analyzed visit records for heterosexual African American men who underwent HIV testing while attending sexually transmitted disease clinics in Baltimore, Maryland, from 1993 to 2000. They used multivariable binomial regression to evaluate associations between circumcision and the risk of HIV infection among visits by patients with known and unknown HIV exposure. Overall, 1096 (2.7%) of 40,571 clinic visits yielded positive HIV test results. Among 394 visits by patients with known HIV exposure, circumcision was significantly associated with lower HIV prevalence (10.2% vs. 22.0%; adjusted prevalence rate ratio [PRR], 0.49 [95% confidence interval [CI], 0.26-0.93]). Conversely, among 40,177 visits by patients with unknown HIV exposure, circumcision was not associated with reduced HIV prevalence (2.5% vs. 3.3%; adjusted PRR, 1.00 [95% CI, 0.86-1.15]), and age ≥ 25 years old and diagnosis of ulcerative sexually transmitted disease were associated with increased prevalence. Circumcision was associated with substantially reduced HIV risk in patients with known HIV exposure, suggesting that results of other studies demonstrating reduced HIV risk for circumcision among heterosexual men likely can be generalized to the US context. **Editors' note: The men in this analysis were African Americans who did not inject drugs, reported sex only with women, and underwent HIV testing during their clinic visit. 394 visits were made by men who were named as sexual contacts of HIV-infected people in the previous year. HIV prevalence was more than 4 times that found at visits of patients with sex**

partners of unknown HIV status. At the visits of HIV-exposed men who were circumcised, there was a significant 51% reduction in HIV prevalence after adjusting for behavioural and demographic characteristics. This suggests that the compelling results of the African trials can be generalised to the US context for heterosexual African-American men.

Begley EB, Jafa K, Voetsch AC, Heffelfinger JD, Borkowf CB, Sullivan PS. Willingness of men who have sex with men (MSM) in the United States to be circumcised as adults to reduce the risk of HIV infection. *PLoS ONE*. 2008;3(7):e2731.

Circumcision reduces HIV acquisition among heterosexual men in Africa, but it is unclear if circumcision may reduce HIV acquisition among men who have sex with men in the United States, or whether men who have sex with men would be willing to be circumcised if recommended. Begley and colleagues interviewed presumed-HIV negative men who have sex with men at gay pride events in 2006. They asked uncircumcised respondents about willingness to be circumcised if it were proven to reduce risk of HIV among men who have sex with men and perceived barriers to circumcision. Multivariate logistic regression was used to identify covariates associated with willingness to be circumcised. Of 780 men who have sex with men, 133 (17%) were uncircumcised. Of these, 71 (53%) were willing to be circumcised. Willingness was associated with black race (exact odds ratio [OR]: 3.4, 95% confidence interval [CI]: 1.3-9.8), non-injection drug use (OR: 6.1, 95% CI: 1.8-23.7) and perceived reduced risk of penile cancer (OR: 4.7, 95% CI:2.0-11.9). The most commonly endorsed concerns about circumcision were post-surgical pain and wound infection. Over half of uncircumcised men who have sex with men, especially black men who have sex with men, expressed willingness to be circumcised. Perceived risks and benefits of circumcision should be a part of educational materials if circumcision is recommended for men who have sex with men in the United States. **Editors' note: Among the male US population born between 1940 and 1990, 73% of African Americans and 88% of Caucasian Americans have been circumcised, usually at birth. Neonatal circumcision reduces the risk of penile cancer, acquisition of many sexually transmitted diseases, incidence of urinary tract infections in infants, and cervical cancer diagnoses in female sexual partners. No randomised controlled trials have been conducted to assess whether circumcision at any age reduces the risk of HIV acquisition in men who have sex with men, presumably for the insertive men. Nonetheless, as this innovative survey at gay pride events reveals, there would be considerable interest among American men who have sex with men if male circumcision were found to confer significant levels of protection in this population.**

10. Paediatric diagnosis

Ngo-Giang-Huong N, Khamduang W, Leurent B, Collins I, Nantasen I, Leechanachai P, Sirirungsi W, Limtrakul A, Leusaree T, Comeau AM, Lallemand M, Jourdain G. Early HIV-1 Diagnosis Using In-House Real-Time PCR Amplification on Dried Blood Spots for Infants in Remote and Resource-Limited Settings. *J Acquir Immune Defic Syndr*. 2008. [Epub ahead of print]

In resource-limited settings, most perinatally HIV-1-infected infants do not receive timely antiretroviral therapy because early HIV-1 diagnosis is not available or affordable. To assess the performance of a low-cost in-house real-time polymerase chain reaction assay to detect HIV-1 DNA in infant dried blood spots. One thousand three hundred nineteen dried blood spots collected throughout Thailand from non-breast-fed infants born to HIV-1-infected mothers were shipped at room temperature to a central laboratory. In-house real-time DNA polymerase chain reaction results were compared with Roche Amplicor HIV-1 DNA test

(Version 1.5) results. In addition, Ngo-Giang-Huong and colleagues verified the Roche test performance on dried blood spots sampled from 1218 other infants using as reference HIV serology result at 18 months of age. Real-time DNA polymerase chain reaction and Roche DNA polymerase chain reaction results were 100% concordant. Compared with HIV serology results, the Roche test sensitivity was 98.6% (95% confidence interval: 92.6% to 100.0%) and its specificity at 4 months of age was 99.7% (95% confidence interval: 99.2% to 99.9%). In-house real-time polymerase chain reaction performed as well as the Roche test in detecting HIV-1 DNA on dried blood spots in Thailand. Combined use of dried blood spots and real-time PCR assays is a reliable and affordable tool to expand access to early HIV-1 diagnosis in remote and resource-limited settings, enabling timely treatment for HIV-1-infected infants. **Editors' note: After drying overnight, dried blood spots (DBS) of only 50 microlitres of blood, obtained through a heelstick procedure, can be sent through the mail from rural and remote settings. This first report of the excellent performance of an in-house real-time HIV DNA polymerase chain reaction (PCR) test, on DBS specimens from non-breast-fed infants of HIV-positive mothers, holds promise for early detection of HIV infection in infants. Real-time PCR assays have high sensitivity and specificity, provide results more rapidly, avoid crossover PCR contamination, and are increasingly affordable. All HIV-infected infants should start on antiretroviral treatment as soon as they are diagnosed because of very high mortality in the first year of life. This highlights the importance of rapid turnaround of DBS results from the testing laboratory back to the clinic.**

Brown E, Chi BH, Read JS, Taha TE, Sharma U, Hoffman IF, Pikora C, Goldenberg R, Fiscus SA. Determining an optimal testing strategy for infants at risk for mother-to-child transmission of HIV-1 during the late postnatal period. *AIDS*. 2008;22(17):2341-6.

To determine the optimal time for a second HIV-1 nucleic acid amplification assay to detect late postnatal transmission of HIV-1 (first negative test at 4-8 weeks of age) in resource-limited settings, Brown and colleagues conducted a longitudinal analysis of data from HIV Prevention Trial Network trial 024. Children born to HIV-1-infected mothers enrolled in the HIV Prevention Trial Network trial 024 were tested for HIV-1 infection at six intervals within the first year of life. Mothers and infants received nevirapine prophylaxis. The authors estimated the probability of being alive and having a positive test in each interval after 4-8 weeks and at 30 days after weaning, conditional on having acquired HIV during the late postnatal period. The interval with the highest probability was taken to be the optimal visit interval. A total of 1609 infants from HIV Prevention Trial Network trial 024 had at least one HIV-1 diagnostic test and were included in the analysis. They found that testing at 1 month after weaning or 12 months of age (whichever comes first) identified 81% of those infected during the late postnatal period (after 4-8 weeks) through breastfeeding. In total, 93% (95% confidence interval 89, 98) of all infected infants would be detected if tests were performed at these two time points. In resource-limited settings, HIV-1 polymerase chain reaction testing at 4-8 weeks followed by a second test at 1 month after weaning or at 1 year of age (whichever comes first), led to the identification of the vast majority of HIV-1-infected infants. **Editors' note: Infants breastfed by their HIV-positive mothers may become infected even though they may have escaped HIV transmission during pregnancy, labour, and delivery. It is important that their HIV infection be diagnosed as soon as possible after it occurs so that they can start on antiretroviral treatment to delay disease progression. This study showed that polymerase chain reaction (PCR)**

testing at 4 to 8 weeks of age, at the time of a routine infant vaccination visit, would detect HIV infection in infants infected in utero, peripartum, or through early breast milk transmission. Repeating the test 1 month after breastfeeding ceases or at age 12 months, whichever ever comes first, would identify an additional 12% of infected infants, bringing to 93% the proportion of infants with HIV infection detected in a timely fashion.

Iloff P, Ntozini R, Nathoo K, Piwoz E, Moulton L; The ZVITAMBO Study Group*, Humphrey J. Making a working clinical diagnosis of HIV infection in infants in Zimbabwe. *Trop Med Int Health*. 2008;13(12):1459-1469.

Clinical algorithms can be helpful in decisions about treatment and feeding options in infancy, but have had limited exposure to real data. This analysis uses data from a large clinical trial to test such algorithms, and thereby develop a successor which performs usefully in poor countries with high HIV-prevalence. The ZVITAMBO trial followed 14 110 mother-baby pairs through infancy. 32% of mothers were HIV-positive. Infants were HIV tested regularly using DNA polymerase chain reaction. Clinical signs were evaluated in terms of identifying HIV-infection at 6 weeks, 6 and 12 months, using Zimbabwean, South African, and WHO generic adaptations of the WHO integrated management of childhood illness HIV algorithm. A modification, in which HIV-exposed infants are first divided into being at least or less than median weight-for-age, was derived and evaluated. At 6 weeks 65% of all infected babies are less than median weight-for-age. Adding at least two clinical signs reduces sensitivity to 20% but those identified are 1.5 (95% CI 1.1-2.1) times more likely to die by 6 months than other infected infants. At 6 months, 86% of uninfected babies of HIV-infected mothers can be identified by selecting those whose weight is greater than median or, if less than median, who exhibit <2 clinical signs. In poor settings a simple clinical algorithm can identify children with probable HIV infection, especially those at risk of early death, who can then be referred for further testing and care, including highly active antiretroviral therapy. Most infants who are HIV-uninfected can be identified at 6 months and provided with support to maintain infection-free survival, including focussed infant-feeding counselling. **Editors' note: When access to HIV testing is limited to antibody testing, laboratory diagnosis of HIV infection in infants is impossible because of the presence of maternal antibodies that cross the placenta during pregnancy. Correlating DNA polymerase chain reaction (PCR) results with clinical signs in this large study, allowed construction of a simple clinical algorithm starting with weight-for-age at 6 weeks. 'Median weight-for-age' means 50% are above and 50% are below a middle mark of weight at a given age. At 6 weeks of age, 65% of HIV-infected babies were below the median, indicating the need for closer follow-up to identify signs and symptoms suggestive of HIV infection. It is not ideal by any means, but it could help get some infants on life-prolonging treatment earlier.**

11. Universal access

Calmy A, Pizzocolo C, Pizarro L, Brücker G, Murphy R, Katlama C; Strategies in Resource-Limited Settings Working Group. The marriage of science and optimized HIV care in resource-limited settings. *AIDS*. 2008;22(17):2227-30.

Large-scale HIV management in resource-limited settings has been remarkably successful in a relatively short time frame. Once combination antiretroviral therapy became more universally available, national treatment programs were able to provide much of the needed

therapy, originally prioritized towards patients with the most advanced and symptomatic disease. The current worldwide expansion of antiretroviral therapy is due to a large broad-based international effort in financing the antiretroviral drugs and infrastructure required for delivering treatment and care. The fears that HIV treatment would detract from other healthcare concerns or lead to widespread drug resistance have been unfounded but important treatment-related issues remain to be addressed immediately by relevant scientific communities. The fundamental scientific concerns fall into two categories: the comprehensive approach to care and treatment management in settings in which resources are limited, and the diversity of a variety of populations who are predominantly women, have heterogeneous viral subtypes and have exposure to different environmental co-pathogens. There is an urgent need to link science and clinical practice wherever it is taking place. We need to learn more about optimal treatment choices and monitoring schemes appropriate in diverse resource-limited settings. Relevant clinical data that are urgently needed include drug efficacy in genetically diverse populations, the most cost-effective and efficient monitoring of therapy, and interactions with drugs to treat common co-infections and diseases. Transfer of competencies must be done as this is essential for operational research. In addition, we must promote and strengthen national reference centres and develop high level skills for the next generation of scientists and clinicians. The international scientific community must address this urgent need with academic, social, scientific, and economic support for the necessary critical research and training so desperately needed. **Editors' note: This is an urgent call for more science, more science capacity-building, and more operational research competencies transfer to enable clinical data collection, monitoring, analysis, and evaluation at the service of improved care. Key questions to address include how to improve adherence, when to switch therapies, optimal treatment for pregnant women, and important drug-drug interactions with anti-tuberculosis and anti-malarial agents.**

Perez F, Aung KD, Ndoro T, Engelsmann B, Dabis F. Participation of traditional birth attendants in prevention of mother-to-child transmission of HIV services in two rural districts in Zimbabwe: a feasibility study. *BMC Public Health*. 2008;8(1):401. [Epub ahead of print]

Prevention of mother-to-child transmission of HIV is among the key HIV prevention strategies in Zimbabwe. A decrease in use of antenatal care services with an increase in home deliveries is affecting the coverage of prevention of mother-to-child transmission interventions in a context of accelerated economic crisis. The main objective was to evaluate acceptability and feasibility of reinforcing the role of traditional birth attendants in family and child health services through their participation in prevention of mother-to-child transmission programmes in Zimbabwe. A community based cross-sectional survey was undertaken using multistage cluster sampling in two rural districts through interviews and focus group discussions among women who delivered at home with a traditional birth attendant, those who had an institutional delivery and traditional birth attendants. 45% of traditional birth attendants interviewed knew the principles of prevention of mother-to-child transmission and 8% delivered a woman with known HIV-positive status in previous year. Of the complete package of prevention of mother-to-child transmission services, more than 75% of traditional birth attendants agreed to participate in most activities with the exception of performing a blood test (17%), accompanying new-borns to closest health centre to receive medication (15%), and assisting health centres in documentation of the link between antenatal care and prevention of mother-to-child transmission services (18%). Women who

delivered at home were less likely to have received more than one antenatal care service or have had contact with a health centre compared to women who delivered in a health centre (91.0% vs 72.6%; $P<0.001$). Also, 63.6% of the women who delivered in a health centre had the opportunity to choose the place of delivery compared to 39.4% of women who delivered at home ($P<0.001$). More than 85% of women agreed that traditional birth attendants could participate in all activities related to a prevention of mother-to-child transmission programme with the exception of performing a blood test for HIV. Concerns were highlighted regarding confidentiality of the HIV-serostatus of women. Although the long-term goal of antenatal care service delivery in Zimbabwe remains the provision of skilled delivery attendance, prevention of mother-to-child transmission programmes will benefit from complementary approaches to prevent missed opportunities. Traditional birth attendants are willing to expand their scope of work regarding activities related to prevention of mother-to-child transmission. There is a need to reinforce their knowledge on mother-to-child transmission prevention measures and better integrate them into the health system. **Editors' note: When health professionals are not available, traditional birth attendants, usually elderly, married or widowed women with a minimum level of education, are a significant workforce in maternity care in high HIV prevalence settings. Legitimising and acknowledging their practice, training them to preserve confidentiality and support women in the process of disclosure to access HIV prevention and treatment programmes, integrating them into prevention of mother-to-child transmission programmes, and conducting operational research to assess their impact are key steps. Reaching the two-thirds of pregnant women with HIV infection who are not currently reached by prevention of mother-to-child transmission programmes is the objective and all able hands need to be on deck.**

12. Cost-effectiveness

Paltiel AD, Freedberg KA, Scott CA, Schackman BR, Losina E, Wang B, Seage Iii GR, Sloan CE, Sax PE, Walensky RP. HIV Preexposure Prophylaxis in the United States: Impact on Lifetime Infection Risk, Clinical Outcomes, and Cost-Effectiveness. *Clin Infect Dis*. 2009;48(6):806-815.

The combination of tenofovir and emtricitabine shows promise as HIV preexposure prophylaxis (PrEP). Paltiel and colleagues sought to forecast clinical, epidemiologic, and economic outcomes of PrEP, taking into account uncertainties regarding efficacy, the risks of developing drug resistance and toxicity, behavioural disinhibition, and drug costs. They adapted a computer simulation of HIV acquisition, detection, and care to model PrEP among men who have sex with men and are at high risk of HIV infection (i.e., 1.6% mean annual incidence of HIV infection) in the United States. Base-case assumptions included 50% PrEP efficacy and monthly tenofovir-emtricitabine costs of \$753. They used sensitivity analyses to examine the stability of results and to identify critical input parameters. In a cohort with a mean age of 34 years, PrEP reduced lifetime HIV infection risk from 44% to 25% and increased mean life expectancy from 39.9 to 40.7 years (21.7 to 22.2 discounted quality-adjusted life-years). Discounted mean lifetime treatment costs increased from \$81,100 to \$232,700 per person, indicating an incremental cost-effectiveness ratio of \$298,000 per quality-adjusted life-year gained. Markedly larger reductions in lifetime infection risk (from 44% to 6%) were observed with the assumption of greater (90%) PrEP efficacy. More-favourable incremental cost-effectiveness ratios were obtained by targeting younger populations with a higher incidence of infection and by improvements in the efficacy and cost of PrEP. PrEP could substantially reduce the incidence of HIV transmission in populations at

high risk of HIV infection in the United States. Although it is unlikely to confer sufficient benefits to justify the current costs of tenofovir-emtricitabine, price reductions and/or increases in efficacy could make PrEP a cost-effective option in younger populations or populations at higher risk of infection. Given recent disappointments in HIV infection prevention and vaccine development, additional study of PrEP-based HIV prevention is warranted. **Editors' note: To date, evidence from animal studies indicates promise for pre-exposure prophylaxis (PrEP) but none of the eight oral and/or topical PrEP trials planned or currently underway in a variety of populations have reported results. Based on current treatment costs for tenofovir-emtricitabine and conservative estimates of efficacy, PrEP is an unattractive option from a US-based cost-effectiveness perspective but reduced costs and increased efficacy would improve the incremental cost-effectiveness ratio (dollars per quality adjusted life years [QALYs] gained). Now let's get some real data to inform such modelling!**

13. Prevention of mother-to-child transmission

Ciaranello AL, Seage GR 3rd, Freedberg KA, Weinstein MC, Lockman S, Walensky RP. Antiretroviral drugs for preventing mother-to-child transmission of HIV in sub-Saharan Africa: balancing efficacy and infant toxicity. *AIDS*. 2008;22(17):2359-69.

Antiretroviral drugs can prevent mother-to-child transmission of HIV infection, but in-utero antiretroviral exposure may be associated with neurologic symptoms due to mitochondrial toxicity. Ciaranello and colleagues sought to identify the currently recommended regimen to prevent mother-to-child transmission that optimally balances risks of pediatric HIV infection and neurologic mitochondrial toxicity. Published mother-to-child transmission and mitochondrial toxicity data were used in a decision analytic model of mother-to-child transmission among women in sub-Saharan Africa. The authors investigated the HIV and mitochondrial toxicity risks associated with no antiretroviral prophylaxis and five recommended regimens ranging from single-dose nevirapine to three-drug antiretroviral therapy. Sensitivity analyses varied all parameters, including infant feeding strategy and the disability of mitochondrial toxicity relative to HIV. Provision of no antiretroviral drugs is the least effective and least toxic strategy, with 18-month HIV risk of 30.4% and mitochondrial toxicity risk of 0.2% (breastfed infants). With increasing drug number and duration, HIV risk decreases markedly (to 4.9% with three-drug antiretroviral therapy), but mitochondrial toxicity risk also increases (to 2.2%, also with three-drug antiretroviral therapy). Despite increased toxicity, three-drug antiretroviral therapy minimizes total adverse pediatric outcomes (HIV plus mitochondrial toxicity), unless the highest published risks are true for both HIV and mitochondrial toxicity, or the disability from mitochondrial toxicity exceeds 6.4 times that of HIV infection. The risk of paediatric mitochondrial toxicity from effective regimens to prevent mother-to-child transmission is at least an order of magnitude lower than the risk of HIV infection associated with less-effective regimens. Concern regarding mitochondrial toxicity should not currently limit the use of three-drug antiretroviral therapy to prevent mother-to-child transmission where it is available. **Editors' note: This modelling showed that protease inhibitor (PI) based 3 drug antiretroviral regimens (ZDV, 3TC, PI) resulted in fewer paediatric infections, slightly more cases of paediatric mitochondrial toxicity, and substantially fewer adverse paediatric outcomes than less toxic but less effective regimens. The true prevalence and severity of infant neurological dysfunction related to mitochondrial toxicity remains unknown. Such toxicity is thought to be due primarily to in utero exposure to NRTI**

(nucleoside reverse transcriptase inhibitors), however maternal HIV viraemia also appears to be an independent risk factor for foetal mitochondrial dysfunction. Whether there will be next generation effects for the foetuses exposed to NRTI, as was seen for women whose mothers used diethylstilbestrol in the 1950s to prevent threatened abortions and unknowingly placed their daughters at higher risk of vaginal cancer, will not be known for a decade or two.

14. Country responses: government and university collaborations

L.P. Babichi, W.J. Bicknell, L. Culpepper B.W. Jack, M.W. Phooko, B. Smith & T.T. Thahane. Institutional commitment and HIV/AIDS: Lessons from the first 3 years of the Lesotho. *Global Public Health*, 2008; 3(4): 417-432.

In mid-2003, Boston University made a decade long institutional commitment to collaborate with the Government of Lesotho as it grappled with the human resource implications of the HIV epidemic. The collaboration is a work in progress. Babichi and colleagues explore the rationale for the University's commitment, detail the development of the relationship between the Government and the University, review the principles that guide the collaboration, report on the activities, results, and challenges to date, and conclude with a look toward the future. They stress the importance of six principles: trust, mutual respect, shared interests, a long time horizon, sustainability, and a country-driven agenda. Although technical or programme content is important, long-term results of value are difficult to achieve if these principles are not honoured. **Editors' note: This collaboration followed the 'country first, donor follows' principle with a collaborative, interactive, open-ended, non-predetermined 10-day assessment of Lesotho's needs and Boston University's areas of relevant strength. The latter's commitment is long-term and university-wide, engaging university resources as well as external donor funds. The collaboration is characterised by a long time-horizon and a focus on sustainability, excellence, relevance, trust, respect, and openness. These are all essential to maintaining a long-term mutual commitment to effectively addressing the root problems affecting delivery of quality HIV prevention, treatment, and care and support services in Lesotho.**

That was *HIV this week*, signing off.

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