

HIV This Week: what scientific journals said

Welcome to issue fifty-three of *HIV This Week*! In this issue, we cover **pre-exposure prophylaxis** (it works in macaques but would you inject yourself daily or before sex to prevent HIV?), **blood borne transmission** (debunking the tetanus toxoid injection - HIV link in 7 African countries; penile modification in young Thai men: get ready to be surprised), **epidemiology** ('Rhodes or roads' at the heart of the HIV epidemic in southern Africa; the rising HIV disease burden in Uganda), **education** (time to act: time trends reveal reversal with less education increasing HIV risk), **basic science** (the CCR5-Delta32 HIV resistance allele is a new explanation for low HIV prevalence in Tunisia; what on earth are membrane nanotubes?), **herpes simplex virus-2** (20th century genital herpes likely kick-started the HIV epidemic in Africa), **impact on society** (grandmothers' productivity is a force to be reckoned with in Botswana; increased tea plucking days on antiretroviral treatment in Kenya), **treatment and care** (it's better to be young when you start on antiretroviral treatment; standard '2 nukes - 1 non-nuke' first-line regimens are cost-effective and work longer), **mortality trends** (population mortality starts falling within months of introduction of antiretroviral treatment in Malawi), **discordant couples** (a prevention imperative: at 12 sites in eastern and southern Africa, 49% of couples with HIV are discordant), **male circumcision** (modelling the impact of male circumcision on women as well as men), and **drug resistance surveillance** (what is threshold survey analysis?; tracking early warning indicators in Malawi).

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1. *Pre-exposure prophylaxis*

García-Lerma JG, Otten RA, Qari SH, Jackson E, Cong ME, Masciotra S, Luo W, Kim C, Adams DR, Monsour M, Lipscomb J, Johnson JA, Delinsky D, Schinazi RF, Janssen R, Folks TM, Heneine W. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. *PLoS Med.* 2008; 5(2):e28.

In the absence of an effective vaccine, HIV continues to spread globally, emphasizing the need for novel strategies to limit its transmission. Pre-exposure prophylaxis (PrEP) with antiretroviral drugs could prove to be an effective intervention strategy if highly efficacious and cost-effective PrEP modalities are identified. García-Lerma and colleagues evaluated daily and intermittent PrEP regimens of increasing antiviral activity in a macaque model that closely resembles human transmission. The authors used a repeat-exposure macaque model with 14 weekly rectal simian HIV challenges. Three drug treatments were given once daily, each to a different group of six rhesus macaques. Group 1 was treated subcutaneously with a human-equivalent dose of emtricitabine (FTC), group 2 received orally the human-equivalent dosing of both FTC and tenofovir-disoproxil fumarate (TDF), and group 3 received subcutaneously a similar dosing of FTC and a higher dose of tenofovir. A fourth group of six rhesus macaques (group 4) received intermittently a PrEP regimen similar to group 3 only 2 h before and 24 h after each weekly virus challenge. Results were compared to 18 control macaques that did not receive any drug treatment. The risk of infection in macaques treated in groups 1 and 2 was 3.8- and 7.8-fold lower than in untreated macaques ($p = 0.02$ and $p = 0.008$, respectively). All six macaques in group 3 were protected. Breakthrough infections had blunted acute viremias; drug resistance was seen in two of six animals. All six animals in group 4 that received intermittent PrEP were protected. This model suggests that single drugs for daily PrEP can be protective but a combination of antiretroviral drugs may be required to increase the level of protection. Short but potent intermittent PrEP can provide protection comparable to that of daily PrEP in this simian HIV/macaque model. These findings support PrEP trials for HIV prevention in humans and identify promising PrEP modalities. **Editors' note: None of the macaques receiving a combination of emtricitabine (FTC) and high dose tenofovir (TDF) either daily or only around the time of exposure to a weekly rectal challenge with SIV became infected. The six macaques that did become infected in the other two active (drug-exposed) arms had a lower viral set point suggesting that the risk of onward transmission during primary infection could be less. These are promising findings in an animal model, however drug resistance in two animals suggest that transmission of resistant virus would be a concern. Furthermore, whether people would be willing to inject themselves subcutaneously either on a daily basis or before a likely exposure remains to be seen. There are six trials in the field now using oral TDF or TDF/FTC with results of the first trial expected in 2008.**

2. Blood borne transmission

de Walque D. Do unsafe tetanus toxoid injections play a significant role in the transmission of HIV/AIDS? Evidence from seven African countries. *Sex Transm Infect.* 2008 ;84(2):122-5.

Although sexual transmission is generally considered to be the main factor driving the HIV epidemic in Africa, recent studies have claimed that iatrogenic transmission should be considered as an important source of HIV infection. In particular, receipt of tetanus toxoid injections during pregnancy has been reported to be associated with HIV infection in Kenya. The objective of this paper is to assess the robustness of this association among women in nationally representative HIV surveys in seven African countries. The association between prophylactic tetanus toxoid injections during pregnancy and HIV infection was analysed, using individual-level data from women who gave birth in the past five years. These data are from the nationally representative Demographic and Health Surveys, which included HIV testing in seven African countries: Burkina Faso 2003 (N = 2424), Cameroon 2004 (N =

2600), Ethiopia 2005 (N = 2886), Ghana 2003 (N = 2560), Kenya 2003 (N = 1617), Lesotho 2004 (N = 1278) and Senegal 2005 (N = 2126). Once the odds ratios (OR) were adjusted for five-year age groups and for ethnic, urban and regional indicators, the association between prophylactic tetanus toxoid injections during pregnancy and HIV infection was never statistically significant in any of the seven countries. Only in Cameroon was there an association between previous tetanus toxoid injection and HIV positivity but it became weaker (OR 1.53, 95% CI 0.91 to 2.57) once urban location and ethnic group were adjusted for. Although the risk of HIV infection through unsafe injections and healthcare should not be ignored and should be reduced, it does not seem that there is, at present and in the seven countries studied, strong evidence supporting the claim that unsafe tetanus toxoid injections are a major factor driving the HIV epidemic. **Editors' note: After simple adjustment for age, location, and ethnicity in these Demographic and Health Survey datasets from seven countries, there were no correlations found between tetanus toxoid injections during pregnancy and HIV infection. Injection safety is important in healthcare settings in Africa, as it is everywhere, but it should not detract from concerted efforts to address the main mode of HIV transmission in these countries – sexual transmission.**

Thomson N, Sutcliffe CG, Sirirojn B, Sintupat K, Aramrattana A, Samuels A, Celentano DD. Penile Modification in Young Thai Men: Risk Environments, Procedures and Wide Spread Implications for HIV and Sexually Transmitted Infections. *Sex Transm Infect.* 2008 Jan 11.

Thomson and colleagues aimed to determine the prevalence and types of penile modification and describe the circumstances surrounding this practice among a sample of young methamphetamine users in Thailand. A mixed methods study was conducted in Chiang Mai, Thailand in 2005-6. One hundred young men were surveyed for the quantitative study and in-depth interviews were administered to 9 men, 11 women and 1 transgender. The prevalence of penile modification was 51%, with the most common type being inlaying with muk(s) (61%). The majority of modifications were performed in prison or juvenile detention (80%) by a friend (90%). Motivations for penile modification included peer pressure and perceived enhanced female sexual pleasure. In prison, the practice was veiled in secrecy, the conditions under which modification was performed were unhygienic, sometimes leading to infection, and sharing equipment was common. Men and women reported that condom use was more difficult post modification as condoms were more likely to break or leak and less likely to fit correctly. In addition, sexual intercourse was often painful for the female partner. In conclusion, penile modification is prevalent in this group of young methamphetamine users and is associated with behaviours and consequences that could facilitate the spread of HIV and other sexually transmitted infections. **Editors' note: Penile modification practices in Thailand date back to the fourteenth century among the aristocracy but today are associated with prisons, the army, and the working class. Over half of one hundred consecutive male participants in a trial to reduce harms associated with methamphetamine use had penile modifications that had been performed in unhygienic settings. The risk of infection, including with blood borne pathogens transmitted through sharing of equipment at the time of the procedure, painful intercourse with trauma experienced by the receptive partner during intercourse, and condom breakage/leakage all raise concerns of increased risk for HIV acquisition and transmission.**

3. Epidemiology

Hargrove, John. Migration, mines and mores: the HIV epidemic in southern Africa. *South Afr J Sci.* 2008: Volume 104, Issue 1 & 2:53-61.

The seriousness of the HIV epidemic in southern and eastern Africa has its roots in the 19th century - in the employment practices instituted on mines, farms and in cities, where millions of men have, ever since, lived apart from their families for the greater part of each year. This destruction of the family unit was a sociological disaster waiting for the arrival of HIV and is the source of many other social ills - not least the increasingly violent nature of South African society. In the short term we can promote HIV prevention measures such as male circumcision and condom use. In the medium term, we can hope that the many billions already spent on microbicide and vaccine research begin to pay dividends. In the long term, we need to change fundamentally the way that people live. **Editors' note: Hargrove cogently argues that it is "Rhodes not roads", i.e. that it was the colonial migratory labour practices that fragmented families and severely compromised family coherence that were the critical determinants at the heart of the southern Africa epidemic. His unavoidable conclusion is that, in addition to intensifying HIV prevention and treatment, we must urgently rebuild family structures in southern and eastern Africa if the HIV epidemic and many other problems having similar sociological determinants are to be dealt with effectively.**

Hladik W, Musinguzi J, Kirungi W, Opio A, Stover J, Kaharuzza F, Bunnell R, Kafuko J, Mermin J. The estimated burden of HIV/AIDS in Uganda, 2005-2010. *AIDS.* 2008; 19; 22(4):503-10.

Hladik and colleagues aimed to estimate the burden of HIV disease in Uganda and the effect of HIV control programmes to mitigate it. The authors performed mathematical modelling and projecting using surveillance and census data. Using antenatal clinic surveillance (1986-2002) and a recent population-based survey (2004-2005) data, they modelled the adult national HIV prevalence over time (1981-2004), and kept prevalence constant at 6.4% for the years 2004-2010. Using Spectrum software and census data, they estimated the national burden of HIV disease and the effect of selected HIV-related prevention and treatment programmes. In 2005, they estimated that there were 135,300 new HIV infections (adult HIV incidence 0.96%), 691,900 asymptomatic prevalent infections, 88 100 AIDS cases, and 76 400 AIDS deaths. An estimated 647,000 (80%) HIV-infected adults were unaware of their infection; one third of all adult deaths were HIV related. As a result of population growth, by 2008 a similar number of people will be HIV infected (1.1 million) as during the peak of the epidemic in 1994. Although antiretroviral therapy coverage is expected to rise from 67,000 (2005) to 160,000 (2010), the number of persons needing but not receiving antiretroviral therapy will decrease only slightly from 127,600 (2005) to 111,100 (2010). The use of single-dose in 2005 nevirapine probably averted only 4% of the estimated 20 400 vertical infections. In conclusion, HIV continues to be a leading cause of adult disease and death in Uganda. Universal antiretroviral therapy access is probably unachievable. With the absolute burden of HIV disease approaching the historic peak in the early 1990s, more effective prevention programmes are of paramount importance. **Editors' note: Although HIV prevalence has declined significantly since the mid-1990s in Uganda, a country with one of the oldest epidemics in the world, the burden of HIV remains high. An important majority of people living with HIV are unaware of their HIV status and therefore are not being evaluated for treatment initiation. New HIV infections that continue to outpace AIDS deaths mean that the total number of people living with HIV this year will reach the 1994 historic peak of 1.1 million people living with HIV, all of whom will**

eventually need treatment. This is no time for Uganda, and other countries reporting declines in HIV transmission in specific populations, to rest on its laurels. Continued treatment scale-up accompanied by intensified, evidence-informed prevention are urgently needed.

4. Education

Hargreaves JR, Bonell CP, Boler T, Boccia D, Birdthistle I, Fletcher A, Pronyk PM, Glynn JR. Systematic review exploring time trends in the association between educational attainment and risk of HIV infection in sub-Saharan Africa. *AIDS*. 2008; 30; 22(3):403-14.

Hargreaves and colleagues aimed to assess the evidence that the association between educational attainment and risk of HIV infection is changing over time in sub-Saharan Africa. The authors conducted a systematic review of published peer-reviewed articles. Articles were identified that reported original data comparing individually measured educational attainment and HIV status among at least 300 individuals representative of the general population of countries or regions of sub-Saharan Africa. Statistical analyses were required to adjust for potential confounders but not over-adjust for variables on the causal pathway. Approximately 4000 abstracts and 1200 full papers were reviewed. Thirty-six articles were included in the study, containing data on 72 discrete populations from 11 countries between 1987 and 2003, representing over 200,000 individuals. Studies on data collected prior to 1996 generally found either no association or the highest risk of HIV infection among the most educated. Studies conducted from 1996 onwards were more likely to find a lower risk of HIV infection among the most educated. Where data over time were available, HIV prevalence fell more consistently among highly educated groups than among less educated groups, in whom HIV prevalence sometimes rose while overall population prevalence was falling. In several populations, associations suggesting greater HIV risk in the more educated at earlier time points were replaced by weaker associations later. HIV infections appear to be shifting towards higher prevalence among the least educated in sub-Saharan Africa, reversing previous patterns. Policy responses that ensure HIV-prevention measures reach all strata of society and increase education levels are urgently needed. **Editors' note: Although data were available from only 11 countries, the findings are supported by evidence of behaviour change as well as theoretical plausibility. The 'diffusion of innovations' model would predict information seeking and adoption of new practices, such as condom use, by more-educated, more-empowered members of a population. This strongly suggests that larger reductions in HIV incidence can be achieved by improving school enrolment, such as through abolition of primary school fees (as has been done in Kenya, Malawi, Tanzania, and Uganda), and tailoring HIV prevention programmes for socially vulnerable groups, while creating positive social environments which reinforce safer HIV prevention behavioural norms across the population.**

5. Basic science

Jlizi A, Edouard J, Fadhlouzi-Zid K, Frigi S, Debré P, Slim A, Theodorou I, El Gaaied AB, Carpentier W. Identification of the CCR5-Delta32 HIV resistance allele and new mutations of the CCR5 gene in different Tunisian populations. *Hum Immunol*. 2007 ;68(12):993-1000.

Polymorphisms in some chemokine receptor genes are associated with susceptibility to and progression of human immunodeficiency virus-1 (HIV-1) infection. Most mutations detected in the CC-chemokine receptor 5 (CCR5) gene are specific to different populations. In this study, Jlizi and colleagues focused on polymorphisms of the CCR5 coding region in three

healthy populations from Tunisia, corresponding to a cosmopolitan population from Tunis, and two isolated Berber populations. In addition to the CCR5-Delta32 deletion, eleven single nucleotide polymorphisms were detected. Some of these point mutations were associated with the same genotype and even the same haplotype. The (L55Q-C101X), I124, V131F, T143N, A159V, I237, T239A and G301R alleles have not been described previously, whereas the CCR5-Delta32, L55Q, A335V and Y339F variants have already been reported in the literature. The distribution and frequency of these variants were different among the three groups studied, a result in agreement with the mosaic genetic structure of the Tunisian population. To determine whether these alleles affect HIV-1 transmission, the authors compared allele frequencies between healthy and HIV-1 infected individuals from Tunis. The frequency of the CCR5-Delta32 variant was significantly different between the two groups, leading us to conclude that this mutation might confer protection against HIV infection in Tunisian populations. **Editors' note: CCR5-Delta32 produces a truncated protein affecting CCR5 gene expression and function and is associated with resistance to HIV infection and slower disease progression. In this study, CCR5-Delta32 was the most frequent variant found in healthy individuals (frequency 0.034) but not found at all in infected individuals. Furthermore, the CCR5-Delta32 mutant was present in the Tunisian population at its highest frequency among Arab countries. The authors speculate that even this low frequency of genetic difference may combine with male circumcision, religious customs, and social norms to explain the low incidence of HIV infection in Tunisia. Additional studies are needed to confirm this interesting hypothesis.**

Sowinski S, Jolly C, Berninghausen O, Purbhoo MA, Chauveau A, Köhler K, Oddos S, Eissmann P, Brodsky FM, Hopkins C, Onfelt B, Sattentau Q, Davis DM. Membrane nanotubes physically connect T cells over long distances presenting a novel route for HIV-1 transmission. *Nat Cell Biol.* 2008 ;10(2):211-9.

Transmission of HIV-1 via intercellular connections has been estimated as 100-1000 times more efficient than a cell-free process, perhaps in part explaining persistent viral spread in the presence of neutralizing antibodies. Such effective intercellular transfer of HIV-1 could occur through virological synapses or target-cell filopodia connected to infected cells. Here Sowinski and colleagues report that membrane nanotubes, formed when T cells make contact and subsequently part, provide a new route for HIV-1 transmission. Membrane nanotubes are known to connect various cell types, including neuronal and immune cells, and allow calcium-mediated signals to spread between connected myeloid cells. However, T-cell nanotubes are distinct from open-ended membranous tethers between other cell types, as a dynamic junction persists within T-cell nanotubes or at their contact with cell bodies. The authors also report that an extracellular matrix scaffold allows T-cell nanotubes to adopt variably shaped contours. HIV-1 transfers to uninfected T cells through nanotubes in a receptor-dependent manner. These data lead us to propose that HIV-1 can spread using nanotubular connections formed by short-term intercellular unions in which T cells specialize. **Editors' note: Transfer of HIV-1 via nanotubes that create physical connections between T cells minimize exposure of the virus to extracellular antibodies, permitting it to escape an important immune defence. This may help explain the virulence and pathogenicity of HIV-1; it also suggests a new avenue for drug targets.**

6. *Herpes simplex virus-2*

Abu-Raddad LJ, Magaret AS, Celum C, Wald A, Longini IM Jr, Self SG, Corey L. Genital herpes has played a more important role than any other sexually transmitted infection in driving HIV prevalence in Africa. *PLoS ONE*. 2008; 3(5):e2230.

Extensive evidence from observational studies suggests a role for genital herpes in the HIV epidemic. A number of herpes vaccines are under development and several trials of the efficacy of HSV-2 treatment with acyclovir in reducing HIV acquisition, transmission, and disease progression have just reported their results or will report their results in the next year. The potential impact of these interventions requires a quantitative assessment of the magnitude of the synergy between HIV and HSV-2 at the population level. A deterministic compartmental model of HIV and HSV-2 dynamics and interactions was constructed. The nature of the epidemiologic synergy was explored qualitatively and quantitatively and compared to other sexually transmitted infections. The results suggest a more substantial role for HSV-2 in fuelling HIV spread in sub-Saharan Africa than other sexually transmitted infections. Abu-Raddad and colleagues estimate that in settings of high HSV-2 prevalence, such as Kisumu, Kenya, more than a quarter of incident HIV infections may have been attributed directly to HSV-2. HSV-2 has also contributed considerably to the onward transmission of HIV by increasing the pool of HIV-positive persons in the population and may explain one-third of the differential HIV prevalence among the cities of the Four Cities study. Conversely, the authors estimate that HIV had only a small net impact on HSV-2 prevalence. In conclusion, HSV-2's role as a biological cofactor in HIV acquisition and transmission may have contributed substantially to HIV particularly by facilitating HIV spread among the low-risk population with stable long-term sexual partnerships. This finding suggests that prevention of HSV-2 infection through a prophylactic vaccine may be an effective intervention both in nascent epidemics with high HIV incidence in the high risk groups, and in established epidemics where a large portion of HIV transmission occurs in stable partnerships. **Editors' note: The herpes simplex-2 (HSV-2) epidemic in sub-Saharan Africa appears to have started in the first half of the twentieth century and reached its peak at about 50% prevalence prior to the HIV epidemic. Now the two viruses are happy bedfellows with HSV-2 increasing HIV acquisition and transmission more than HIV increases HSV-2 acquisition and transmission. This synergy has allowed HIV to reach a higher proportion of the general population than would have been possible without this biological interaction. An effective HSV-2 vaccine is urgently needed to protect all young people in established epidemics before sexual debut, but there is no doubt that it would be beneficial worldwide.**

7. *Impact on society*

Bock J, Johnson. Grandmothers' Productivity and the HIV/AIDS Pandemic in sub-Saharan Africa. *J Cross Cult Gerontol*. 2008 Jan 8.

The human immunodeficiency virus (HIV) pandemic has left large numbers of orphans in sub-Saharan Africa. Botswana has an HIV prevalence rate of approximately 40% in adults. Morbidity and mortality are high, and in a population of a 1.3 million there are nearly 50,000 children who have lost one or both parents to HIV. The extended family, particularly grandparents, absorbs much of the childrearing responsibilities. This creates large amounts of additional work for grandmothers especially. The embodied capital model and the grandmother hypothesis are both derived from life history theory within evolutionary ecology, and both predict that one important factor in the evolution of the human extended

family structure is that post-reproductive individuals such as grandmothers provide substantial support to their grandchildren's survival. Data collected in the pre-pandemic context in a traditional multi-ethnic community in the Okavango Delta of Botswana are analyzed to calculate the amount of work effort provided to a household by women of different ages. Results show that the contributions of older and younger women to the household in term of both productivity and childrearing are qualitatively and quantitatively different. These results indicate that it is unrealistic to expect older women to be able to compensate for the loss of younger women's contributions to the household, and that interventions be specifically designed to support older women based on the type of activities in which they engage that affect child survival, growth, and development. **Editors' note: This study found that grandmothers are unable to substitute their labour for that of younger women lost to the family because of the energy intensity (strength and stamina) required for grain-processing. Further, the more time they allocate to food production, the less time they have for seeking and processing traditional wild foods that provide high levels of micronutrients and phytochemicals. They also can no longer produce traditional craft items such as the baskets, fishing implements, and tools essential to the productivity of all members of the household. Critically, their grandchildren have no means to acquire the skills and knowledge about traditional activities from them that are key to their long-term survival. Interventions to compensate for lost labour should support grandmothers in pursuing their traditional roles and activities.**

Larson BA, Fox MP, Rosen S, Bii M, Sigei C, Shaffer D, Sawe F, Wasunna M, Simon JL. Early effects of antiretroviral therapy on work performance: preliminary results from a cohort study of Kenyan agricultural workers. *AIDS*. 2008; 22(3):421-5.

This paper estimates the impact of antiretroviral therapy on days harvesting tea per month for tea-estate workers in Kenya. Such information is needed to assess the potential economic benefits of providing treatment to working adults. Data for this analysis come from company payroll records for 59 HIV-infected workers and a comparison group of all workers assigned to the same work teams (reference group, n = 1992) for a period covering 2 years before and 1 year after initiating antiretroviral therapy. Mean difference tests were used to obtain overall trends in days harvesting tea by month. A difference in difference approach was used to estimate the impact of HIV on days working in the pre-antiretroviral therapy period. Information on likely trends in the absence of the therapy was used to estimate the positive impacts on days harvesting tea over the initial 12 months on antiretroviral therapy. No significant difference existed in days plucking tea each month until the ninth month before initiating antiretroviral therapy, when workers worked -2.79 fewer days than references (15% less). This difference grew to 5.09 fewer days (27% less) in the final month before initiating antiretroviral therapy. After 12 months on antiretroviral therapy, Larson and colleagues conservatively estimate that workers worked at least twice as many days in the month than they would have in the absence of antiretroviral therapy. In conclusion treatment had a large, positive impact on the ability of workers to undertake their primary work activity, harvesting tea, in the first year on antiretroviral therapy. **Editors' note: This study found that tea pluckers placed on antiretroviral treatment worked 7.5 to 9.5 days more harvesting tea in month 12 than they would have worked in the absence of antiretroviral treatment. A large cohort and a longer period of follow-up are required to determine the impact of antiretroviral treatment on work performance over the long term but these are promising initial findings.**

8. Treatment and care

Micheloud D, Berenguer J, Bellón JM, Miralles P, Cosin J, de Quiros JC, Conde MS, Muñoz-Fernández MA, Resino S. Negative influence of age on CD4+ cell recovery after highly active antiretroviral therapy in naive HIV-1-infected patients with severe immunodeficiency. *J Infect.* 2008 ;56(2):130-6.

Micheloud and colleagues aimed to study the effect of age on several outcomes among 187 antiretroviral-naive infected patients who started highly active antiretroviral therapy (HAART) with ≤ 200 CD4(+)/microl. The authors carried out a retrospective study to determine the hazard ratio (HR) to reach an outcome in patients who experienced a change from the baseline in CD4(+) counts of at least +100, +200, +300, +400 and +500 cells/microl at any moment during the follow-up and the odds ratio (OR) of achieving and maintaining a CD4(+) value above a certain setpoint during at least 6, 12 or 18 months. The adjusted HR for an increase of +400 CD4(+)/microl and +500 CD4(+)/microl were 1.3 (95% CI: 1.1; 1.5) and 1.3 (95% CI: 1.1; 1.6) times slower for each additional 5 years of age at baseline. In addition, for every 5 years of extra age, the adjusted OR to achieve an absolute CD4(+) cell count > 500 /microl at 6, 12 and 18 months after the initiation of HAART were 2.2 (95% CI: 1.5; 3.2), 1.8 (95% CI: 1.2; 2.6), and 1.8 (95% CI: 1.2; 2.9) times less likely, respectively. The authors also found that patients ≥ 45 years old had worse complete CD4(+) recovery (CD4(+) > 500 cells/microl) than patients < 45 years old. In conclusion, the CD4(+) recovery after HAART is a prolonged and continuous process which extends for several years. Age at baseline is inversely correlated with the magnitude and speed of CD4(+) recovery among HIV-1 infected patients. **Editors' note: Older age at the time of HIV acquisition is associated with faster disease progression. This study found that increasing age was associated with slower CD4 count recovery after initiation of antiretroviral treatment and a lower likelihood of reaching an absolute CD4 count of 500. This suggests that older people may benefit from earlier initiation of antiretroviral treatment before CD4 counts reach 200.**

Beck EJ, Mandalia S, Youle M, Brettle R, Fisher M, Gompels M, Kinghorn G, McCarron B, Pozniak A, Tang A, Walsh J, Williams I, Gazzard B. Treatment outcome and cost-effectiveness of different highly active antiretroviral therapy regimens in the UK (1996-2002). *Int J STD AIDS.* 2008; 19(5):297-304.

The aim of this study was to estimate the outcome and cost-effectiveness per life-year-gained (LYG) of first-, second- and third-line non-nucleoside reverse transcriptase inhibitors (NNRTI) versus protease inhibitor (PI) containing highly active antiretroviral therapy regimens. Hospital care costs (2002 US dollars discounted 3.5% per annum) were linked to treatment failure times. Results show that the median time-to-treatment failure for first-line (nucleoside reverse transcriptase inhibitors) 2NRTIs + NNRTI was substantially longer than that for 2NRTIs + PI (boosted), 2NRTIs + PI and 2NRTIs + 2PIs, whereas for second- and third-line they were similar. Comparing first-line 2NRTIs + NNRTI with 2NRTIs + PI (boosted) cost per LYG was US\$ 12,375; US\$ 12,139 per LYG when compared with 2NRTIs + PI and US\$ 2948 per LYG when compared with 2NRTIs + 2PIs. For second-line cost per LYG comparing 2NRTIs + NNRTI with 2NRTIs + PI (boosted) was US\$ 19,501; US\$ 18,364 per LYG when compared with 2NRTIs + PI and cost-saving when compared with 2NRTIs + 2PIs. For third-line cost per LYG comparing 2NRTIs + NNRTI with 2NRTIs + PI(boosted) was US\$ 2708; US\$ 11,559 per LYG when compared with 2NRTIs + PI and cost-saving when compared with 2NRTIs + 2PIs. In conclusion, first-line 2NRTIs + NNRTI was cost-effective or cost-

saving when compared with PI-containing regimens for all lines of therapy. Such information is required by clinicians and managers of HIV services to make appropriate treatment decisions based on clinical and financial grounds, and given the increasing number of people living with HIV, such information will become more important over time. **Editors' note: In low- and middle-income countries, the standard first-line therapy recommended by the WHO public health approach contains a backbone of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (2 nukes and 1 non-nuke). Until now, the outcome and cost-effectiveness of such regimens compared to protease inhibitor (PI) containing regimens have not been studied. Although the setting for this study is a high-income country, the 2 nukes-1 non-nuke first-line, second-line, and third-line regimens were either cost-effective or cost-saving. Of note is the much longer median time to treatment failure for people on these first-line regimens compared to those containing protease inhibitors, a finding of direct relevance for low- and middle-income countries.**

9. Mortality Trends

Jahn A, Floyd S, Crampin AC, Mwaungulu F, Mvula H, Munthali F, McGrath N, Mwafilaso J, Mwinuka V, Mangongo B, Fine PE, Zaba B, Glynn JR. Population-level effect of HIV on adult mortality and early evidence of reversal after introduction of antiretroviral therapy in Malawi. *Lancet*. 2008;371(9624):1603-11.

Malawi, which has about 80,000 deaths from AIDS every year, made free antiretroviral therapy available to more than 80 000 patients between 2004 and 2006. Jahn and colleagues aimed to investigate mortality in a population before and after the introduction of free antiretroviral therapy, and therefore to assess the effects of such programmes on survival at the population level. The authors used a demographic surveillance system to measure mortality in a population of 32,000 in northern Malawi, from August, 2002, when free antiretroviral therapy was not available in the study district, until February, 2006, 8 months after a clinic opened. Causes of death were established through verbal autopsies (retrospective interviews). Patients who registered for antiretroviral therapy at the clinic were identified and linked to the population under surveillance. Trends in mortality were analysed by age, sex, cause of death, and zone of residence. Before antiretroviral therapy became available in June, 2005, mortality in adults (aged 15-59 years) was 9.8 deaths for 1000 person-years of observation (95% CI 8.9-10.9). The probability of dying between the ages of 15 and 60 years was 43% (39-49) for men and 43% (38-47) for women; 229 of 352 deaths (65.1%) were attributed to AIDS. 8 months after the clinic that provided antiretroviral therapy opened, 107 adults from the study population had accessed treatment, out of an estimated 334 in need of treatment. Overall mortality in adults had decreased by 10% from 10.2 to 8.7 deaths for 1000 person-years of observation (adjusted rate ratio 0.90, 95% CI 0.70-1.14). Mortality was reduced by 35% (adjusted rate ratio 0.65, 0.46-0.92) in adults near the main road, where mortality before antiretroviral therapy was highest (from 13.2 to 8.5 deaths per 1000 person-years of observation before and after antiretroviral therapy). Mortality in adults aged 60 years or older did not change. The findings of a reduction in mortality in adults aged between 15 and 59 years, with no change in those older than 60 years, suggests that deaths from AIDS were averted by the rapid scale-up of free antiretroviral therapy in rural Malawi, which led to a decline in adult mortality that was detectable at the population level. **Editors' note: With no vital registration system in place or reliable mortality statistics reported from health services, this study**

established a continuous registration demographic surveillance system after completing a household census in Karonga district (pop. 32,000). A child born into this population before the introduction of antiretroviral therapy had a 37% lifetime risk of dying from AIDS. This surveillance system demonstrated that by 8 months after the free antiretroviral treatment programme began, overall mortality in adults aged 15-59 had decreased by 10%. Only a third of adults in need of treatment had been started on antiretroviral treatment so population mortality should continue to fall as access to treatment is decentralized and scaled up.

10. *Discordant couples*

Lingappa JR, Lambdin B, Bukusi EA, Ngure K, Kavuma L, Inambao M, Kanweka W, Allen S, Kiarie JN, Makhema J, Were E, Manongi R, Coetzee D, de Bruyn G, Delany-Moretlwe S, Margaret A, Mugo N, Mujugira A, Ndase P, Celum C; for the Partners in Prevention HSV-2/HIV Transmission Study Group. Regional Differences in Prevalence of HIV-1 Discordance in Africa and Enrollment of HIV-1 Discordant Couples into an HIV-1 Prevention Trial. *PLoS ONE*. 2008; 3(1):e1411.

Most HIV-1 transmission in Africa occurs among HIV-1-discordant couples (one partner HIV-1 infected and one uninfected) who are unaware of their discordant HIV-1 serostatus. Given the high HIV-1 incidence among HIV-1 discordant couples and to assess efficacy of interventions for reducing HIV-1 transmission, HIV-1 discordant couples represent a critical target population for HIV-1 prevention interventions and prevention trials. Substantial regional differences exist in HIV-1 prevalence in Africa, but regional differences in HIV-1 discordance among African couples, has not previously been reported. The Partners in Prevention herpes simplex virus type 2 (HSV-2)/HIV-1 Transmission Trial ("Partners HSV-2 Study"), the first large HIV-1 prevention trial in Africa involving HIV-1 discordant couples, completed enrolment in May 2007. Partners HSV-2 Study recruitment data from 12 sites from East and Southern Africa were used to assess HIV-1 discordance among couples accessing couples HIV-1 counselling and testing, and to correlate with enrolment of HIV-1 discordant couples. HIV-1 discordance at Partners HSV-2 Study sites ranged from 8-31% of couples tested from the community. Across all study sites and, among all couples with one HIV-1 infected partner, almost half (49%) of couples were HIV-1 discordant. Site-specific monthly enrolment of HIV-1 discordant couples into the clinical trial was not directly associated with prevalence of HIV-1 discordance, but was modestly correlated with national HIV-1 counselling and testing rates and access to palliative care/basic health care ($r = 0.74$, $p = 0.09$). In conclusion, HIV-1 discordant couples are a critical target for HIV-1 prevention in Africa. In addition to community prevalence of HIV-1 discordance, national infrastructure for HIV-1 testing and healthcare delivery and effective community outreach strategies impact recruitment of HIV-1 discordant couples into HIV-1 prevention trials. **Editors' note:** In the screening phase for a large trial assessing the impact of herpes simplex-2 (HSV-2) suppression with acyclovir in co-infected (HIV-1, HSV-2) partners of HIV-negative, HSV-2 negative people, 51,900 couples were tested. Among all the couples tested in which HIV infection was found, 36 to 85% of them, depending on the study site, were discordant with an overall rate of 49%. Because discordant couples are such an important population for HIV prevention (in reality, HIV prevalence is 50% in the couple's bed), community mobilisation to encourage couples to be tested as couples, rather than as individuals, and to provide social support to couples who learn their discordant or positive concordant status is an urgent public health priority.

11. Male circumcision

Hallett TB, Singh K, Smith JA, White RG, Abu-Raddad LJ, Garnett GP. Understanding the impact of male circumcision interventions on the spread of HIV in Southern Africa. *PLoS ONE*. 2008; 3(5):e2212.

Three randomised controlled trials have clearly shown that circumcision of adult men reduces the chance that they acquire HIV infection. However, the potential impact of circumcision programmes--either alone or in combination with other established approaches--is not known and no further field trials are planned. Hallett and colleagues have used a mathematical model, parameterised using existing trial findings, to understand and predict the impact of circumcision programmes at the population level. The results indicate that circumcision will lead to reductions in incidence for women and uncircumcised men, as well as those circumcised, but that even the most effective intervention is unlikely to completely stem the spread of the virus. Without additional interventions, HIV incidence could eventually be reduced by 25-35%, depending on the level of coverage achieved and whether onward transmission from circumcised men is also reduced. However, circumcision interventions can act synergistically with other types of prevention programmes, and if efforts to change behaviour are increased in parallel with the scale-up of circumcision services, then dramatic reductions in HIV incidence could be achieved. In the long-term, this could lead to reduced AIDS deaths and less need for anti-retroviral therapy. Any increases in risk behaviours following circumcision, i.e. 'risk compensation', could offset some of the potential benefit of the intervention, especially for women, but only very large increases would lead to more infections overall. Circumcision will not be the silver bullet to prevent HIV transmission, but interventions could help to substantially protect men and women from infection, especially in combination with other approaches. **Editors' note: As this modelling study confirms, male circumcision can not and should not be a standalone HIV prevention strategy but rather part of a combination prevention strategy that increases choices for people. Since all methods, other than sexual abstinence, are partially protective, people should aim to combine methods for increased protection. This modelling study also estimates the potential impact for women, the subject of an important consultation being convened by WHO, UNAIDS, UNICEF, and UNFPA in Mombasa, Kenya, June 24-25 2008.**

12. Drug resistance surveillance

Bennett D, Myatt M, Bertagnolio S, Sutherland D, Gilks C. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. *Antivir Ther* 2008; Supplement 2: 25-36.

The World Health Organization (WHO) HIV drug resistance threshold survey method was developed for surveillance of transmitted HIV drug resistance in resource-limited countries. The method is being implemented with minimal resources as a routine public health activity to produce comparable results in multiple countries and areas within countries. Transmitted drug resistant HIV strains will be seen first in cities or health districts where antiretroviral treatment has been widely available for years. WHO recommends countries begin surveillance in these areas. Each survey requires <=47 specimens from individuals consecutively diagnosed with HIV to categorize resistance to each relevant drug class as <5%, 5-15% or >15%. Use of routinely collected information and remnant specimens is

recommended to minimize costs. Site and individual eligibility criteria are designed to minimize inclusion of antiretroviral drug-experienced individuals and individuals infected before antiretroviral treatment was available. Surveys have been implemented in 21 countries. In this supplement, seven countries report results of <5% transmitted HIV drug resistance in areas where antiretroviral treatment has been available for the longest time period. The main challenges in implementation are acquiring sufficient numbers of eligible specimens and optimizing specimen handling. The WHO HIV drug resistance threshold survey method is feasible in resource-limited countries and produces information relevant to antiretroviral treatment and drug resistance prevention planning. **Editors' note: This supplement contains reports of HIV drug resistance surveillance from seven countries (Ethiopia, Malawi, Swaziland, Tanzania, Vietnam, South Africa, and Thailand) along with methodological articles explaining the threshold survey analysis method. This method requires minimal infrastructure and provides important information to limit the emergence and transmission of resistance in resource-limited settings.**

Hedt B, Wadonda-Kabondo N, Makombe S, Harries A, Schouten E, Limbambala E, Hochgesang M, Aberle-Grasse J, Kamoto K. Early warning indicators for HIV drug resistance in Malawi. *Antivir Ther* 2008; Supplement 2: 69-75.

Malawi started rapid scale-up of antiretroviral therapy in 2004 and by December 2006 had initiated over 85,000 patients on treatment. Early warning indicator reports can help to minimize the risk of emerging drug resistance. Data collected during the routine quarterly supervision of 103 public sector sites was used to compile the first early warning indicator report for HIV drug resistance in Malawi, reflecting outcomes for October to December 2006. All sites reach the World Health Organization (WHO) targets for prescribing practices and drug supply continuity. The target for adherence was achieved by 85% of sites and 84% achieved the target for minimizing treatment defaults; however, less than half of all sites reach the WHO target for patient retention. In conclusion, these results emphasize the importance of defaulter tracing and initiating treatment earlier in the course of HIV infection. As part of a comprehensive HIV drug resistance monitoring programme, the Ministry of Health plans for on-going tracking of these indicators, as well as special data collection from the private sector. Plans are also underway to gather information on other recommended indicators that are not collected during routine supervision. **Editors' note: In Malawi, data on programmatic factors associated with an increased risk of drug resistance such as patient adherence, prescribing practices, continuity of drug supply, and patient outcomes are reviewed with site personnel during routine quarterly supervision visits. National patient mastercards (the patient record) and patient antiretroviral registers are complimented by pharmacy registers. With monthly targets for new patients starting HIV treatment set nationally, drug procurement can be accurately estimated and drugs reallocated if necessary to prevent the stock-outs that are a prominent cause of drug resistance.**

That was *HIV This Week*, signing off.

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