

HIV This Week: what scientific journals said

Welcome to the 78th issue of **HIV This Week**! In this issue, we cover the following topics:

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1. Faith-based responses

Islam and harm reduction.

Kamarulzaman A, Saifuddeen SM. Int J Drug Policy.2009.Dec [Epub ahead of print].

Although drugs are haram and therefore prohibited in Islam, illicit drug use is widespread in many Islamic countries throughout the world. In the last several years increased prevalence of this problem has been observed in many of these countries which has in turn led to increasing injecting drug use driven HIV epidemics across the Islamic world. Whilst some countries have recently responded to the threat through the implementation of harm reduction programmes, many others have been slow to respond. In Islam, The Quran and the Prophetic traditions or the Sunnah are the central sources of references for the laws and principles that guide the Muslims' way of life and by which policies and guidelines for responses including that of contemporary social and health problems can be derived. **The preservation and protection of the dignity of man, and steering mankind away from harm and destruction are central to the teachings of Islam.** When viewed through the **Islamic principles of the preservation and protection of the faith, life, intellect, progeny and wealth, harm reduction programmes are permissible** and in fact provide a **practical solution** to a problem that could result in far greater damage to the society at large if left unaddressed.

For abstract access click here:

http://www.ncbi.nlm.nih.gov/pubmed/20006483?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_Res ultsPanel.Pubmed_RVDocSum&ordinalpos=2

Editors' note: Following an in-depth tour of the epidemiology of illicit drug consumption, injecting drug use, and the HIV epidemic in Islamic countries, this paper presents the basic guidelines provided in the Quran and the Sunnah (Prophetic traditions) that support needle exchange programmes and opioid substitution therapy. The pragmatic evidence-informed public health approach of harm reduction programmes in the Islamic Republic of Iran, Malaysia and Indonesia contrasts starkly with the rejection of harm reduction in Libya, Tunisia, Syria, and Jordan. Despite the tenets of Islam, resistance in the latter countries appears ideological with roots in a criminal justice perspective. As the authors underscore, harm reduction is a public health issue that not only does not violate shariah law, it follows Islamic principles.

2. Resources/impact development

Factors influencing global antiretroviral procurement prices.

Wirtz VJ, Forsythe S, Valencia-Mendoza A, Bautista-Arredondo S. BMC Public Health. 2009. 9 Suppl 1:S6.

Antiretroviral medicines are one of the most costly parts of HIV treatment. Many countries are struggling to provide universal access to antiretroviral medicines for all people living with HIV. Although substantial price reductions of antiretroviral medicines have occurred, especially between 2002 and 2008, achieving sustainable access for the next several decades remains a major challenge for most low- and middle-income countries. The objectives of the present study were twofold: first, to analyze global antiretroviral prices between 2005 and 2008 and associated factors, particularly procurement methods and key donor policies on antiretroviral procurement efficiency; second, to discuss the options of procurement processes and policies that should be considered when implementing or reforming access to antiretroviral treatment programs. An antiretroviral medicines price-analysis was carried out using the **Global Price Reporting Mechanism from the World Health Organization**. For a selection of 12 antiretrovirals, global median prices and price variation were calculated. Linear regression models for each antiretroviral were used to identify factors that were associated with lower procurement prices. Logistic regression models were used to identify the characteristics of those countries which procure below the highest and lowest direct manufactured costs. **Three key factors appear to have an influence on a country's antiretroviral prices: (a) whether the product is generic or not; (b) the socioeconomic status of the country; (c) whether the country is a member of the**

Clinton HIV/AIDS Initiative. Factors which did not influence procurement below the highest direct manufactured costs were HIV prevalence, procurement volume, whether the country belongs to the least developed countries or a focus country of the United States President's Emergency Plan for AIDS Relief. **One of the principal mechanisms that can help to lower prices for antiretroviral medicines over the next several decades is increasing procurement efficiency. Benchmarking prices** could be one useful tool to achieve this.

For full text access click here: <http://www.biomedcentral.com/1471-2458/9/S1/S6>

Editors' note: There has been an unprecedented global effort to increase antiretroviral drug price transparency, including through the requirements of the Global Fund, the Clinton Initiative, and others for countries to report their pricing data. The Global Price Reporting Mechanism (GPRM) provides information on the prices that countries actually paid for antiretroviral medications through its publicly accessible database <http://www.who.int/hiv/amds/gprm/en/>. Analysis of the GPRM data debunks the assumptions that procuring larger volumes will reduce prices (that was true for only 2 of the 12 drugs studied) and that generic competition leads to equivalent innovator prices (only the second line innovator product lopinavir/ritonavir was associated with lower prices than generic products). Since there is tiered pricing or discounts for most antiretroviral drugs bought by low- and low-middle-income countries, with the exception of the entry inhibitor maraviroc, continued expansion of the GPRM to include data from all countries will increase long-term efficiency (best value for money) in antiretroviral drug procurement.

HIV prevention cost-effectiveness: a systematic review.

Galárraga O, Colchero MA, Wamai RG, Bertozzi SM. *BMC Public Health*. 2009. 9 Suppl 1:S5.

After more than 25 years, public health programs have not been able to sufficiently reduce the number of new HIV infections. Over 7,000 people become infected with HIV every day. Lack of convincing evidence of cost-effectiveness may be one of the reasons why implementation of effective programs is not occurring at sufficient scale. This paper identifies, summarizes and critiques the cost-effectiveness literature related to HIV-prevention interventions in low- and middle-income countries during 2005-2008. Systematic identification of publications was conducted through several methods: electronic databases, internet search of international organizations and major funding/implementing agencies, and journal browsing. Inclusion criteria included: HIV prevention intervention, year for publication (2005-2008), setting (low- and middle-income countries), and cost-effectiveness estimation (empirical or modeling) using **outcomes in terms of cost per HIV infection averted and/or cost per disability-adjusted life year (DALY) or quality-adjusted life year (QALY)**. The authors found 21 distinct studies analyzing the cost-effectiveness of HIV-prevention interventions published in the past four years (2005-2008). **Seventeen cost-effectiveness studies analyzed biomedical interventions; only a few dealt with behavioural and environmental/structural interventions.** Sixteen studies focused on sub-Saharan Africa, and only a handful on Asia, Latin America and Eastern Europe. **Many HIV-prevention interventions are very cost effective in absolute terms (using costs per DALY averted), and also in country-specific relative terms (in cost per DALY measured as percentage of GDP per capita).** There are several types of interventions for which cost-effectiveness studies are still **not available or are insufficient**, including **surveillance, abstinence, school-based education, universal precautions, prevention for positives** and most **structural interventions**. The sparse cost-effectiveness evidence available is not easily comparable; thus, not very useful for decision making. More than 25 years into the HIV epidemic and billions of dollars of spending later, there is still much work to be done both on costs and effectiveness to adequately inform HIV prevention planning.

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Editors' note: Cost-effectiveness analyses in HIV prevention can provide part of the information that decision-makers use to decide on the optimal mix of interventions to tailor to their epidemic context. Although available cost-effectiveness data show that many HIV prevention interventions are cost-effective, there are huge gaps in our knowledge. For example, there are no cost-

effectiveness studies on prevention for and with positive people, for key populations at higher risk of HIV exposure in concentrated epidemics around the world, and for inmates or other captive populations. We lack cost-effectiveness data by epidemic type and scale-up scenario, as well as for a number of HIV prevention interventions that are considered standard components of national strategies. Cost-effectiveness analysis has several limitations and is not the 'be all, end all' in decision-making but it can usefully inform difficult choices.

3. Viral resistance and HIV treatment

Evolutionary Dynamics of Complex Networks of HIV Drug-Resistant Strains: The Case of San Francisco.

Smith R, Okano J, Kahn J, Bodine E, Blower S. *Science*. 2010. Jan. [Epub ahead of print]

Over the past two decades, HIV resistance to antiretrovirals has risen to high levels in the wealthier countries of the world able to afford widespread treatment. The authors have gained insights into the **evolution and transmission dynamics of ARV resistance** by designing a **biologically complex multistrain network model**. Using this model, they traced the **evolutionary history of antiretroviral resistance** in San Francisco and **predict the future dynamics**. Using classification and regression trees, Smith and colleagues have identified the key immunologic, virologic, and treatment factors that increase antiretroviral resistance. Their **modelling shows that 60% of the currently circulating antiretroviral-resistant strains in San Francisco are capable of causing self-sustaining epidemics**, as each individual infected with one of these strains can cause on average more than one new resistant infection. It is possible that a new wave of antiretroviral-resistant strains that pose a significant threat to global public health is emerging.

For abstract access click here: <http://www.sciencemag.org/cgi/content/abstract/science.1180556>

Editors' note: These modellers predict that a wave of NNRTI- (non-nucleoside reverse transcriptase inhibitor) resistant strains will emerge over the next 5 years in San Francisco due to HIV transmission from untreated individuals. They also claim that if the reproduction number (the number of infections that one person transmits) of wild-type strains is reduced below one in resource-constrained settings (which would normally see an epidemic decline), self-sustaining epidemics of NNRTI-resistant strains could arise. Whether their model's predictions are accurate or not remains to be seen but clearly increased investment in resistance monitoring around the world is warranted as we scale up to universal access to antiretroviral treatment for all.

Improved Virological Outcomes in British Columbia Concomitant with Decreasing Incidence of HIV Type 1 Drug Resistance Detection.

Gill V, Lima V, Wen Zhang, Wynhoven B, Yip B, Hogg R, Montaner J, and Harrigan R. *Clinical Infectious Diseases*. 2010. 50:98–105.

There have been limited studies evaluating temporal changes in the incidence of detection of drug resistance among human immunodeficiency virus type 1 (HIV-1) isolates and concomitant changes in plasma HIV load for treated individuals in a population-wide setting. **Longitudinal plasma viral load and genotypic resistance data** were obtained from patients receiving antiretroviral therapy from the British Columbia Drug Treatment Program from July 1996 through December 2008. A total of 24,652 resistance tests were available from 5422 individuals. The incidence of successful plasma viral load suppression and of resistance to each of 3 antiretroviral categories (nucleoside/nucleotide reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors) was calculated for the population receiving therapy. There has been a **drastic decrease in the incidence of new cases of HIV-1 drug resistance in individuals followed during 1996–2008**. In 1997, the incidence rate of any newly detected resistance was 1.73 cases per 100 person-months of therapy, and by 2008, the incidence rate had decreased 112-fold, to 0.13 cases per 100 person-months of therapy. This decrease in the incidence of resistance has occurred at an exponential rate, with halftimes on the order of 2–3 years. Concomitantly, the proportion of individuals with plasma viral load

suppression has increased linearly over time (from 64.7% with HIV RNA levels ≤ 50 copies/mL in 2000 to 87.0% in 2008; $R^2=0.97$; $P < .001$). The authors' results suggest an **increasing effectiveness of antiretroviral therapy at the populational level**. The vast majority of treated patients in British Columbia now have either suppressed plasma viral load or drug-susceptible HIV-1, according to their most recent test results.

[For full text access click here:](#)

<http://www.journals.uchicago.edu/doi/pdf/10.1086/648729?cookieSet=1>

Editors' note: Rather than investigating the prevalence of transmitted drug resistance in the population or the prevalence of acquired drug resistance among people on treatment, these investigators, who were uniquely placed to do so, assessed the incidence of drug resistance over a 12-year period. They found exponential decreases in the incidence rate of drug resistance, including NNRTI (non-nucleoside reverse transcriptase inhibitor) resistance (40-fold decrease), despite increases in annual and cumulative exposure to antiretroviral drugs. These authors conclude that efforts to improve accessibility to antiretroviral treatment have the potential to greatly reduce HIV-1 levels in a population without increasing the risk of drug resistance.

4. Male circumcision

Male circumcision and risk of male-to-female HIV-1 transmission: a multinational prospective study in African HIV-1-serodiscordant couples.

Baeten JM, Donnell D, Kapiga SH, Ronald A, John-Stewart G, Inambao M, Manongi R, Vwalika B, Celum C; for the Partners in Prevention HSV/HIV Transmission Study Team. *AIDS*. 2009. Dec [Epub ahead of print].

Male circumcision reduces female-to-male HIV-1 transmission risk by approximately 60%. Data assessing the effect of circumcision on male-to-female HIV-1 transmission are conflicting, with one observational study among HIV-1-serodiscordant couples showing reduced transmission but a randomized trial suggesting no short-term benefit of circumcision. Data were collected as part of a prospective study among African HIV-1-serodiscordant couples were analyzed for the relationship between circumcision status of HIV-1-seropositive men and risk of HIV-1 acquisition among their female partners. Circumcision status was determined by physical examination. Cox proportional hazards analysis was used. A total of 1096 HIV-1-serodiscordant couples in which the male partner was HIV-1-infected were followed for a median of 18 months; 374 (34%) male partners were circumcised. Sixty-four female partners seroconverted to HIV-1 (incidence 3.8 per 100 person-years). **Circumcision of the male partner was associated with a nonstatistically significant approximately 40% lower risk of HIV-1 acquisition by the female partner** (hazard ratio 0.62, 95% confidence interval 0.35-1.10, $P = 0.10$). The magnitude of this effect was similar when restricted to the subset of HIV-1 transmission events confirmed by viral sequencing to have occurred within the partnership ($n = 50$, hazard ratio 0.57, $P = 0.11$), after adjustment for male partner plasma HIV-1 concentrations (hazard ratio 0.60, $P = 0.13$), and when excluding follow-up time for male partners who initiated antiretroviral therapy (hazard ratio 0.53, $P = 0.07$). Among HIV-1-serodiscordant couples in which the HIV-1-seropositive partner was male, the authors observed no increased risk and potentially decreased risk from circumcision on male-to-female transmission of HIV-1.

[For access to abstract click here:](#)

http://journals.lww.com/aidsonline/Abstract/publishahead/Male_circumcision_and_risk_of_male_to_female_HIV_1.99628.aspx

Editors' note: The trend seen here among 1096 couples toward a protective effect of male circumcision for HIV-negative women in discordant partnerships is intriguing. Sexual behaviours of couples with circumcised men were similar to those in which the man was not circumcised, only genetically-linked transmissions (i.e. transmissions within the couple) were considered (incidence 3.0 per 100 person years), and follow-up time after initiation of antiretroviral treatment (when viral

loads presumably fell) was excluded. The result was a borderline statistically significant 47 per cent reduced risk of HIV-1 acquisition in women. Possible mechanisms that might explain lower risk for women are reduced risk of sexually transmitted infections in circumcised men or reduced likelihood of direct HIV transmission that would have otherwise occurred as a result of microtrauma or inflammation of the foreskin.

The effects of circumcision on the penis microbiome.

Price LB, Liu CM, Johnson KE, Aziz M, Lau MK, Bowers J, Ravel J, Keim PS, Serwadda D, Wawer MJ, Gray RH., *PLoS One*. 2010. 5:e8422.

Circumcision is associated with significant reductions in HIV, HSV-2, and HPV infections among men and significant reductions in bacterial vaginosis among their female partners. The authors assessed the penile (coronal sulci) microbiota in 12 HIV-negative Ugandan men before and after circumcision. Microbiota were characterized using sequence-tagged 16S rRNA gene pyrosequencing targeting the V3-V4 hypervariable regions. Taxonomic classification was performed using the RDP Naïve Bayesian Classifier. Among the **42 unique bacterial families** identified, Pseudomonadaceae and Oxalobacteriaceae were the most abundant irrespective of circumcision status. **Circumcision was associated with a significant change in the overall microbiota** (PerMANOVA $p = 0.007$) and with a **significant decrease in putative anaerobic bacterial families** (Wilcoxon Signed-Rank test $p = 0.014$). Specifically, two families-Clostridiales Family XI ($p = 0.006$) and Prevotellaceae ($p = 0.006$)-were uniquely abundant before circumcision. Within these families they identified a number of anaerobic genera previously associated with bacterial vaginosis including: Anaerococcus spp., Finegoldia spp., Peptoniphilus spp., and Prevotella spp. **The anoxic microenvironment of the subpreputial space may support pro-inflammatory anaerobes that can activate Langerhans cells to present HIV to CD4 cells in draining lymph nodes. Thus, the reduction in putative anaerobic bacteria after circumcision may play a role in protection from HIV and other sexually transmitted diseases.**

[For full text access click here:](#)

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0008422>

Editors' note: Although molecular analyses have been used to characterise the microbiota or microbial community in the vagina, this is the first molecular assessment of the bacterial diversity found in the male genital mucosa. This pre-post circumcision study of 12 men shows that removing the foreskin removes the oxygen-poor environment of the mucosa under the foreskin that provides a warm, moist home for bacteria, many of which are anaerobic and are associated with bacterial vaginosis in women. This helps explain why the female partners of circumcised men have fewer sexually transmitted infections and less bacterial vaginosis. Getting rid of these bacteria through circumcision reduces mucosal inflammation and may provide part of the explanation for the reduced risk of HIV, herpes simplex-2, and human papilloma virus (HPV) infections in circumcised men.

5. Paediatric treatment

Response to planned treatment interruptions in HIV infection varies across childhood

Paediatric European Network for Treatment of AIDS. *AIDS*. 2010. 24:231-41.

The aim of this study was to evaluate clinical, immunological, and virological consequences of CD4-guided antiretroviral therapy planned treatment interruptions compared with continuous therapy in children with chronic HIV infection in the Paediatric European Network for Treatment of AIDS 11 trial. This was a multicentre, 72-week, open, randomized, phase II trial. One hundred and nine children with HIV-RNA below 50 copies/ml and CD4% of at least 30% (2-6 years) or at least 25% and CD4 cell count of at least 500 cells/microl (7-15 years) were **randomized to continuous therapy (53) or planned treatment interruptions (56)**. In planned treatment interruptions, antiretroviral therapy was restarted if confirmed CD4% was less than 20% or more than 48 weeks

had been spent off antiretroviral therapy. The **primary outcome** was Centers for Disease Control and Prevention (CDC) **stage C event, death, or CD4% less than 15%** (and CD4 cell count less than 200 cells/microl for children aged 7-15 years). At baseline, median (interquartile range) age was 9 (6-12) years, CD4% 37% (33-41), CD4 cell count 966 (793-1258) cells/microl, nadir CD4% before combination antiretroviral therapy 18% (10-27), time on antiretroviral therapy 6 (3-6) years, and 26% were CDC stage C. After median (range) 130 (33-180) weeks of follow-up, 4 versus 48% of time was spent off antiretroviral therapy in continuous therapy and planned treatment interruptions, respectively. No child died or had a new CDC stage C event; one (2%) continuous therapy versus four (7%) planned treatment interruptions children had a primary outcome based on CD4%/cell count ($P = 0.2$). **Lower nadir CD4% predicted faster CD4% decline after stopping antiretroviral therapy.** Younger age and higher nadir CD4% predicted being off ART for at least 48 weeks and better CD4% recovery following planned treatment interruptions. In this first paediatric trial of planned treatment interruption, there **were no serious clinical outcomes. Younger children had better CD4% recovery** after planned treatment interruptions. Immunology substudies and long-term follow-up in Paediatric European Network for Treatment of AIDS 11 trial are ongoing. Further research into the role of treatment interruption in children is required, particularly, as guidelines now recommend early antiretroviral therapy for all infected infants.

For abstract access click here:

http://www.ncbi.nlm.nih.gov/pubmed/20010073?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_Res ultsPanel.Pubmed_RVDocSum&ordinalpos=1

Editors' note: After starting antiretroviral treatment, children have a greater potential for immune regeneration than do adults because the thymus is more active in childhood. Furthermore, the risk-benefit balance of lifelong continuous treatment versus planned treatment interruptions in vertically HIV-infected children may be different than for adults, considering the risks of long-term drug toxicity and viral resistance. The encouraging results of this PENTA II pilot study, the first planned treatment interruption trial to take place in children, support continuation of two large treatment interruption trials ongoing in Africa. These are the CHER trial in South Africa studying 400 infants starting antiretroviral treatment before 12 weeks of age and stopping at first or second birthday, and the Bana trial in Botswana of 600 children which has a similar design to PENTA II with different CD4% thresholds for stopping and restarting. Given that it is recommended that all infants start antiretroviral treatment as soon as HIV infection is diagnosed, learning whether planned treatment interruptions are a good idea in children is an important clinical research question.

6. Comorbidity

Utility of a Point-of-Care Malaria Rapid Diagnostic Test for Excluding Malaria as the Cause of Fever among HIV-Positive Adults in Rural Rakai, Uganda.

Mills L, Kagaayi J, Nakigozi G, Galiwango R, Ouma J, Shott J, Ssempijja V, Gray R, Wawer M, Serwadda D, Quinn T, and Reynolds S. Am. J. Trop. Med. Hyg. 2010. 82:145-147.

Mills and colleagues compared results of a **malaria rapid diagnostic test** (Binax Now[®] Malaria, Binax-M, Inverness Medical Innovations, Inc., Waltham, MA) **performed at rural mobile clinics** in Uganda by clinicians evaluating **febrile adult HIV patients to thick smear evaluated at a central laboratory by trained microscopists**. Two hundred forty-six samples were analyzed, including 14 (5.7%) which were thick-smear positive for falciparum malaria. **Sensitivity of Binax-M compared with thick smear was 85.7%** (95% CI: 57.2–98.2), **specificity 97.8%** (95% CI: 94.9–99.3), **positive and negative predictive values were 70.6%** (95% CI: 44.0–89.7) **and 99.1%** (95% CI: 96.8–99.9), respectively. The rapid diagnostic test accurately ruled malaria "in or out" at the point-of-care, facilitating appropriate clinical management and averting unnecessary anti-malarial therapy.

For abstract access click here: <http://www.ajtmh.org/cgi/content/abstract/82/1/145>

Editors' note: Through a PEPFAR-funded mobile HIV clinic programme, most participants in this study in a falciparum malaria endemic district in Uganda had received insecticide treated bed nets, cotrimoxazole prophylaxis regardless of CD4 count, and antiretroviral treatment if their CD4 counts fell below 250 cells/ μ l. With malaria suspected in 41.5% of general out-patient visits in this district, use of this point-of-care test in people living with HIV who presented with fever allowed health care providers to focus on other urgent causes of fever. The test had a high negative predictive value, meaning that a negative test was highly likely to mean that the person did not have malaria.

7. People living with HIV

Suicide in HIV-Infected Individuals and the General Population in Switzerland, 1988-2008.

Keiser O, Spoerri A, Brinkhof MW, Hasse B, Gayet-Ageron A, Tissot F, Christen A, Battegay M, Schmid P, Bernasconi E, Egger M; for the Swiss HIV Cohort Study and the Swiss National Cohort. Am J Psychiatry. 2010. 167:143-150.

High rates of suicide have been described in HIV-infected patients, but it is unclear to what extent the introduction of antiretroviral therapy has affected suicide rates. The authors examined time trends and predictors of suicide in the pre-antiretroviral treatment (1988-1995) and antiretroviral treatment (1996-2008) eras in HIV-infected patients and the general population in Switzerland. The authors analyzed data from the Swiss HIV Cohort Study and the Swiss National Cohort, a longitudinal study of mortality in the Swiss general population. They calculated standardized mortality ratios comparing HIV-infected patients with the general population and used Poisson regression to identify risk factors for suicide. **From 1988 to 2008, 15,275 patients were followed in the Swiss HIV Cohort Study for a median duration of 4.7 years.** Of these, 150 died by suicide (rate 158.4 per 100,000 person-years). In men, standardized mortality ratios declined from 13.7 (95% CI=11.0-17.0) in the pre-antiretroviral treatment era to 3.5 (95% CI=2.5-4.8) in the late antiretroviral treatment era. In women, ratios declined from 11.6 (95% CI=6.4-20.9) to 5.7 (95% CI=3.2-10.3). In both periods, **suicide rates tended to be higher in older patients, in men, in injection drug users, and in patients with advanced clinical stage of HIV illness.** An increase in CD4 cell counts was associated with a reduced risk of suicide. **Suicide rates decreased significantly with the introduction of antiretroviral treatment, but they remain above the rate observed in the general population,** and risk factors for suicide remain similar.

For abstract access click here: <http://ajp.psychiatryonline.org/cgi/content/abstract/167/2/143>

Editors' note: The results of this study, revealing encouraging declines in the suicide rate among people living with HIV in Switzerland since the advent of antiretroviral treatment, need to be seen in context. Swiss suicide rates are in the top-third in Europe and the top quintile, i.e the top 20%, in the world. Declines in the suicide rate have occurred in the general population too but not to the extent seen in surrounding countries. Switzerland has no national suicide prevention programme to address this important public health problem and the suicide rate among people living with HIV, despite the important declines documented here, may be higher than in other European countries. They are certainly higher than in the general Swiss population and are higher than those in other patients with life-threatening conditions. Although 75% of people with HIV who committed suicide had a diagnosis of mental illness, it is unclear to what extent stigma, discrimination, social isolation, drug toxicity, and other factors are playing roles. Understanding what is influencing decisions to commit suicide is the first step to preventing such unnecessary deaths among people living with HIV.

8. HIV testing

Effect of provider-initiated testing and counselling and integration of ART services on access to HIV diagnosis and treatment for children in Lilongwe, Malawi: a pre- post comparison.

Weigel R, Kamthunzi P, Mwansambo C, Phiri S, Kazembe PN. BMC Pediatr. 2009. 9(1):80.

The HIV prevalence in Malawi is 12 % and Kamuzu Central Hospital, in the capital Lilongwe, is the main provider of adult and paediatric HIV services in the central region. The Lighthouse at Kamuzu Central Hospital offers voluntary HIV testing and counselling for adults and children. In June 2004, Lighthouse was the first clinic to provide free antiretroviral treatment in the public sector, but few children accessed the services. In response, provider-initiated HIV testing and counselling and an antiretroviral treatment clinic were introduced at the paediatric department at Kamuzu Central Hospital in Quarter 4 (Q4) 2004. The authors analysed prospectively collected, aggregated data of quarterly reports from Q1 2003 to Q4 2006 from opt-in HIV testing and counselling centre registers, antiretroviral treatment registers and clinic registrations at the antiretroviral treatment clinics of both Lighthouse and the paediatric department. By comparing data of both facilities before (Q1 2003 to Q3 2004), and after the introduction of the services at the paediatric department (Q4 2004 to Q4 2006), they assessed the effect of this intervention on the uptake of HIV services for children at Kamuzu Central Hospital. Overall, 3971 children were tested for HIV, **2428 HIV-infected children were registered for care and 1218 started antiretroviral treatment**. Between the two periods, the median (IQR) number of children being tested, registered and starting antiretroviral treatment per quarter rose from 101 (53-109) to 358 (318-440), 56 (50-82) to 226 (192-234) and 18 (8-23) to 139 (115-150), respectively. The median proportion of tested clients per quarter that were children rose from 3.8% (2.7-4.3) to 9.6% (8.8 to 10.0) ($p=0.0009$) and the proportion of **antiretroviral treatment starters that were children rose from 6.9% (4.9-9.3) to 21.1% (19.2-24.2) ($p=0.0036$)**. The proportion of registered children and adults starting antiretroviral treatment each quarter increased similarly, from 26% to 53%, and 20% to 52%, respectively. Implementation of provider-initiated HIV testing and counselling and integration of antiretroviral treatment services within the paediatric ward are likely to be the main reasons for improved access to HIV testing and counselling and antiretroviral treatment for children at Kamuzu Central Hospital, and can be recommended to other hospitals with paediatric inpatients in resource limited settings with high HIV prevalence.

For full text access click here: <http://www.biomedcentral.com/1471-2431/9/80>

Editors' note: Even though providers initiated an offer of HIV testing and counselling with the caregivers of only 10% of admitted children at the Kamuzu Central Hospital, there was a marked increase in the absolute numbers and proportions of children tested for HIV and started on antiretroviral treatment at this facility, compared to the era of parent/caregiver-initiated voluntary testing and counselling. It is unclear whether this modest increase in provider-initiated testing and counselling made the difference or whether it was the advent of free antiretroviral treatment that changed both client and health worker attitudes towards HIV counselling and testing. In any case, 41% of all children tested at the hospital were tested through the paediatric ward and the yield there was high, providing an additional entry point to antiretroviral treatment for children in Lilongwe.

"It's better not to know": perceived barriers to HIV voluntary counseling and testing among sub-Saharan African migrants in Belgium.

Manirankunda L, Loos J, Alou TA, Colebunders R, Nöstlinger C. AIDS Educ Prev. 2009. 21:582-93.

This study explored perceptions, needs, and barriers of sub-Saharan African migrants in relation to HIV voluntary counselling and testing. Using an inductive qualitative methodological approach, data were obtained from focus group discussions. Results showed that participants were in principle in favour of voluntary counselling and testing. However, they indicated that **barriers outweighed advantages**. Such barriers included **fear of positive test results** and its **related personal and social consequences, lack of information, lack of preventive health behaviour, denial of HIV risk**, and **missed opportunities**. Limited financial resources were only a concern for some subgroups like young people, asylum seekers, and recent migrants. This study identified multiple and intertwined barriers to voluntary counselling and testing from a community perspective. In order to promote voluntary counselling and testing, interventions such as raising awareness through culturally sensitive education should be adopted at community level. At level of service provision, provider initiated HIV testing including target group tailored counselling should be promoted.

Editors' note: This first qualitative community-based study of the barriers to uptake of voluntary counselling and testing among sub-Saharan migrants in Belgium found that previously acquired experiences in their countries of origin negatively influenced testing uptake. The images of relatives or friends, who had been ill and died of AIDS, shaped attitudes toward knowledge of serostatus, as did the considerable responsibilities that many recent migrants have toward family and community members back home. Focus group participants indicated that provider-initiated discussions of HIV testing, combined with the testimonies of people living with HIV and in good health on how to live with HIV, would help reduce fears of HIV testing and counselling. Efforts to reduce stigma, increase social support, and increase testing uptake in a culturally sensitive manner will increase the proportion of migrants wanting to learn their HIV status.

9. Tuberculosis

Recurrent TB: relapse or reinfection? The effect of HIV in a general population cohort in Malawi.

Crampin AC, Mwaungulu JN, Mwaungulu FD, Mwafuilirwa DT, Munthali K, Floyd S, Fine PE, Glynn JR. *AIDS*. 2010 Jan 28;24(3):417-26

The aim of the study was to estimate rates of recurrent tuberculosis due to reinfection and relapse, by HIV status, in a general population. A long-term cohort study was conducted in Karonga district, rural Malawi. All tuberculosis patients with culture-proven disease in Karonga district were followed up after treatment. HIV testing was offered and all Mycobacterium tuberculosis isolates were fingerprinted using IS6110 RFLP. **Fingerprints from initial and recurrent disease episodes were compared to distinguish relapse and reinfection:** a second episode was considered a relapse if the fingerprint was identical or differed by only 1-4 bands and was the first occurrence of that pattern in the population. Rates of and risk factors for recurrence, reinfection disease, and relapse were estimated using survival analysis and Poisson regression. Five hundred and eighty-four culture-positive episodes of tuberculosis were diagnosed and treatment was completed during 1995-2003 in patients with known HIV status; 53 culture-positive recurrences occurred by May 2005. **Paired fingerprints were available for 39 of these. Reinfections accounted for 1/16 recurrences in HIV-negative and 12/23 in HIV-positive individuals. Rates of relapse were similar in HIV-positive and HIV-negative individuals.** Using multiple imputation to allow for missing fingerprint information, **the rate of reinfection disease in HIV-positive individuals was 2.2/100 person-years, and in HIV-negative individuals 0.4/100 person-years. HIV increases the rate of recurrent tuberculosis in this setting by increasing the rate of reinfection disease, not relapse.**

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Editors' note: It appears from this and other studies that a second bout of tuberculosis (TB) in an HIV-negative person in most settings is most likely to be due to relapse and may reflect overall programme effectiveness in treating TB. Relapse rates following successful completion of treatment are highest in the first 6 months off treatment. Although numbers were small, relapse rates in this study were encouragingly similar for HIV-negative and HIV-positive people. The story was much different for re-infection with a rate ratio of 6.3 (1.3-31.5, p=0.02) comparing HIV-positive and HIV-negative individuals. That re-infection occurs at all among HIV-negative people begs the question: if natural infection does not always prevent re-infection, is there still hope for a TB vaccine, at least for some people? The higher risk of re-infection in HIV-positive people, none of them on antiretroviral treatment, suggests that HIV may directly influence the risk of re-infection, increase the risk of development of disease, and/or increase the risk of exposure to other TB strains in health care settings. It is important to untangle the contribution of each of these and to see if antiretroviral treatment scale-up to all HIV-positive patients with TB, along with

environmental controls in TB and HIV clinics, can reduce the risk of re-infection and associated high mortality for people living with HIV.

10. Basic science

Human erythrocytes selectively bind and enrich infectious HIV-1 virions.

Beck Z, Brown BK, Wieczorek L, Peachman KK, Matyas GR, Polonis VR, Rao M, Alving CR. *PLoS One*.2009.4:e8297.

Although CD4(+) cells represent the major target for HIV infection in blood, claims of complement-independent binding of HIV-1 to erythrocytes and the possible role of Duffy blood group antigen, have generated controversy. To examine the question of binding to erythrocytes, HIV-1 was incubated in vitro with erythrocytes from 30 healthy leukapheresis donors, and binding was determined by p24 analysis and adsorption of HIV-1 with reduction of infectivity for CD4(+) target cells. All of the cells, regardless of blood group type, bound HIV-1 p24. A typical preparation of **erythrocytes bound <2.4% of the added p24**, but erythrocytes selectively removed essentially all of the viral infectivity as determined by decreased infection of CD4(+) target cells; however, **cell-associated HIV-1 was approximately 100-fold more efficient, via trans infection, than unadsorbed virus for infection of CD4(+) cells.** All of the bound HIV-1 p24 was released by treatment of the cells with EDTA, and binding was optimized by adding Ca(2+) and Mg(2+) during the washing of erythrocytes containing bound HIV-1. Although the small number of contaminating leukocytes in the erythrocyte preparation also bound HIV-1 p24, there was no significant binding to CD4, and it thus appears that the binding occurred on leukocytes at non-CD4 sites. Furthermore, binding occurred to erythrocyte ghosts from which contaminating leukocytes had been previously removed. The results demonstrate that **erythrocytes incubated in vitro with HIV-1 differentially adsorb all of the infectious HIV-1 virions** (as opposed to non-infectious or degraded virions) **in the absence of complement and independent of blood group**, and **binding is dependent on divalent cations.** By analogy with HIV-1 bound to DC-SIGN on dendritic cells, **erythrocyte-bound HIV-1 might comprise an important surface reservoir for trans-infection of permissive cells.**

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Editors' note: Although the exact mechanism of binding of HIV-1 to erythrocytes remains unknown, there is likely more than one mechanism. This study demonstrates that in the absence of complement which HIV-1 usually activates so that it can bind to complement receptors on cells, HIV-1 binds to erythrocytes, regardless of whether they display Duffy blood group antigen or not. The binding occurs only on the cell surface, permitting erythrocytes with HIV-1 on their surface to present it to CD4+ cells which are not in plentiful supply compared to other cell types. Thus, erythrocytes in the blood may be acting like dendritic cells in tissue to carry and offer HIV-1 to the very target cells that HIV-1 uses for replication, in a process called *trans* infection. This appears likely to be a far more frequent infecting mechanism than direct infection of CD4+ cells by circulating free virus.

11. PrEP

Rearranging retroviral regimens for HIV-intermittent prophylaxis with oral Truvada protects macaques from rectal SHIV Infection

García-Lerma G, Cong M, Mitchell J, Youngpairoj A, Zheng Q, Masciotra S, Martin A, Kuklenyik Z, Holder A, Lipscomb J, Pau C, Barr J, Hanson D, Otten R, Paxton L, Folks T and Heneine W. *Sci Transl Med*. 2010. 2: 14ra4.

Antiretroviral drugs have transformed the lives of HIV-infected people by preventing progression to full-blown AIDS. These drugs also dramatically reduce HIV transmission from mothers to infants during pregnancy and breastfeeding, and work in monkeys suggests that daily doses can also

reduce transmission from unprotected sex. But prophylactic treatment with antiretroviral drugs is costly and impractical—even if confined to a high-risk population. García-Lerma *et al.* now show that **in monkeys a more realistic medication schedule may work just as well as daily doses.** To simulate how people are likely to be infected with HIV, the authors exposed macaque monkeys rectally to **14 weekly doses of simian-human immunodeficiency virus (SHIV) engineered to resemble the human virus.** Control macaques treated in this way became infected within the first five exposures to SHIV. Researchers then assessed whether oral, human-equivalent doses of antiretroviral agents could prevent infection in monkeys. **The best protection—equivalent to that provided by daily antivirals—occurred when the drug Truvada was given 1, 3, or 7 days before virus exposure followed by a second dose 2 hours after exposure. Less effective, but still better than no treatment at all, was a schedule in which the drug was given 2 hours before or after exposure and then again 24 hours later.** Drugs given only 24 or 48 hours after exposure did not safeguard against infection. The results of this study are preliminary, largely because each of the groups had only six macaques, but they are nevertheless promising. If ongoing clinical trials in healthy people show that daily antiretroviral therapy can diminish the chances of acquiring HIV after exposure, a reasonable next step would be to evaluate more practical, less costly drug schedules in humans. For example, a weekly dose followed by a second dose after a possible exposure could prove both effective and tractable. It will also be important to evaluate treatments based solely on exposure, as these would not require ongoing prophylactic drug treatment and would minimize any drug toxicity. If one or more of these therapeutic regimens is successful, antiretroviral drugs may expand the transformation they have already engendered by preventing many more new infections as well as controlling existing ones.

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Editors' note: Despite several limitations of these non-human primate trials, they nonetheless provide food for thought and for human trial design. All the current oral Pre-Exposure Prophylaxis (PrEP) phase IIb and III trials in humans are studying daily administration of either tenofovir (TDF) or a combination of TDF and emtricitabine (FTC). Good complements to each other, FTC appears to have more rapid absorption and tissue distribution while TDF has a long intracellular persistence. Based on these findings of good protection from rectal challenge in macaques given intermittent oral TDF/FTC treatment (varying times before but topping up 2 hours after exposure in active arms), the results of human trials of intermittent PrEP are needed. Intermittent PrEP regimens would likely be easier to adhere to, while decreasing drug costs and probably reducing drug toxicities. Those animals that did become infected appeared to have lower peak levels of virus in the blood. If lower viral set points are confirmed, this may reduce CD4+ cell count depletion and slow disease progression but may also mean less onward transmission. There are many questions to be answered about PrEP before it can be considered as a candidate to join the biomedical component of combination prevention (biomedical, behavioural, structural) strategies. The first question is whether daily administration will prove effective in the current trials of men who have sex with men, people who inject drugs, and heterosexuals at increased risk. If it does, there will be heightened interest in rapidly testing the safety and efficacy of intermittent PrEP in humans to inform policy and programme design decision-making.

12. Epidemiology

Halting HIV/AIDS with avatars and havatars: a virtual world approach to modelling epidemics.

Gordon R, Björklund NK, Smith RJ, Blyden ER. BMC Public Health. 2009;9 Suppl 1:S13.

A major deficit of all approaches to epidemic modelling to date has been the need to approximate or guess at human behaviour in disease-transmission-related contexts. **Avatars are generally human-like figures in virtual computer worlds controlled by human individuals.** The authors introduce the concept of a "havatar", which is a **(human, avatar) pairing.** Evidence is mounting that this pairing behaves in virtual contexts much like the human in the pairing might behave in analogous real-world contexts. Gordon *et al.* propose that **studies of havatars, in a virtual world,**

may give a realistic approximation of human behaviour in real-world contexts. If the virtual world approximates the real world in relevant details (geography, transportation, etc.), virtual epidemics in that world could accurately simulate real-world epidemics. **Havatar modelling of epidemics therefore offers a complementary tool for tackling how best to halt epidemics,** including perhaps HIV, since sexual behaviour is a significant component of some virtual worlds, such as Second Life. Havatars place the control parameters of an epidemic in the hands of each individual. **By providing tools that everyone can understand and use, we could democratise epidemiology.**

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Editors' note: Reviewing current modelling approaches (continuous or deterministic, discrete or individual, and stochastic process modelling), these authors point out that all epidemic modelling second-guesses human behaviour. Their proposition that epidemiological modellers monitor the social networks of havatars ("h" stands for human) to obtain a better representation of real-world disease transmission raises several questions. Although the 13 million people who joined the virtual world Second Life signed waivers that would allow tracking of all transactions, there may be ethical issues to consider when modellers intervene in people's virtual worlds with HIV epidemic simulations to study the behaviour of the avatars under a person's control and make extrapolations to human behaviour. Unleashing invisible, simulated viruses that infect havatars and can be transmitted could cause problems, even if the viruses themselves have no effects such as simulated weight loss or changes in colour. The possibility of virtual world stigma might become real. As well, the people currently part of this virtual world are unlikely to represent populations at higher risk of HIV exposure around the world so the validity of the extrapolations to the HIV epidemic we face today could well be in question.

That was *HIV this week*, signing off.

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