

HIV This Week: what scientific journals said

Welcome to the 71st issue of *HIV This Week*! In this issue, we cover **male circumcision** (does circumcising HIV-infected men reduce transmission to women?; does sex in the wound healing period increase HIV acquisition risk for HIV-negative men?), **programme evaluation: equity** (Malawi leads the way in equity policy and analysis; how sex and income affect survival and retention in Nyanga's antiretroviral treatment programme near Cape Town), **injecting-drug users** (good news on harm reduction in the USA), **paediatric outcomes** (non-infected kids exposed to antiretroviral drugs in pregnancy do not have intrauterine growth retardation; how many kids starting antiretroviral therapy get immune reconstitution inflammatory syndrome (IRIS)?; avoiding disseminated BCG disease means not vaccinating any infant against TB if they are born to an HIV-positive mother until they are found to be uninfected), **health care delivery** (Rwanda measures the effects of integrating HIV clinical services into primary health care; what impact do Global Health Initiatives in Zambia have on human resources for antiretroviral treatment roll-out?), **people living with HIV** (social networks prove a real asset in accessing hard to reach populations in the US), **treatment** (why you shouldn't wait to start antiretroviral treatment if you have an opportunistic infection; fugitive data in a trial of therapeutic drug monitoring), **reproductive health** (jury still out on whether hormonal contraceptives increase HIV disease progression), **basic science** (how common are long-term nonprogressors and HIV controller patients in France?; elite controllers have it easier with inefficient HIV envelope glycoproteins), **resistance** (would circulating HIV drug resistance undermine PrEP among young women in Zimbabwe?; WHO's new surveillance list of drug resistance mutations), **sexual behaviour** (changes in numbers of sexual partners but discrepancies in HIV prevalence persist between sites in South Africa, Zimbabwe and Uganda), and **research financing** (high time to make the pie bigger for neglected disease research and development).

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1. *Male circumcision*

Wawer MJ, Makumbi F, Kigozi G, Serwadda D, Watya S, Nalugoda F, Buwembo D, Ssempijja V, Kiwanuka N, Moulton LH, Sewankambo NK, Reynolds SJ, Quinn TC, Opendi P, Iga B, Ridzon R, Laeyendecker O, Gray RH. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. *Lancet*. 2009 Jul 18;374(9685):229-37.

Observational studies have reported an association between male circumcision and reduced risk of HIV infection in female partners. Wawer and colleagues set out to assess whether circumcision in HIV-infected men would reduce transmission of the virus to female sexual partners. 922 uncircumcised, HIV-infected, asymptomatic men aged 15-49 years with CD4-cell counts 350 cells per microL or more were enrolled in this unblinded, randomised controlled trial in Rakai District, Uganda. Men were randomly assigned by computer-generated randomisation sequence to receive immediate circumcision (intervention; n=474) or circumcision delayed for 24 months (control; n=448). HIV-uninfected female partners of the randomised men were concurrently enrolled (intervention, n=93; control, n=70) and followed up at 6, 12, and 24 months, to assess HIV acquisition by male treatment assignment (primary outcome). A modified intention-to-treat (ITT) analysis, which included all concurrently enrolled couples in which the female partner had at least one follow-up visit over 24 months, assessed female HIV acquisition by use of survival analysis and Cox proportional hazards modelling. This trial is registered with ClinicalTrials.gov, number NCT00124878. The trial was stopped early because of futility. 92 couples in the intervention group and 67 couples in the control group were included in the modified ITT analysis. 17 (18%) women in the intervention group and eight (12%) women in the control group acquired HIV during follow-up (p=0.36). Cumulative probabilities of female HIV infection at 24 months were 21.7% (95% CI 12.7-33.4) in the intervention group and 13.4% (6.7-25.8) in the control group (adjusted hazard ratio 1.49, 95% CI 0.62-3.57; p=0.368). Circumcision of HIV-infected men did not reduce HIV transmission to female partners over 24 months; longer-term effects could not be assessed. Condom use after male circumcision is essential for HIV prevention. **Editors' note: When this trial was stopped for futility because it lacked the power to answer the question of whether or not HIV-positive men who get circumcised are less likely to transmit HIV, it became clear that we would likely never know the definitive answer to this question. However, a key insight gained from the trial is the importance of sexual abstinence until complete wound healing. Premature resumption of sex may delay wound healing, increase the risk that a man may acquire a new HIV infection, and increase the risk of HIV transmission to sexual partners. These researchers previously found that 93% of HIV-positive men circumcised at CD4 > 350 cells were healed by 6 weeks post-circumcision. However, in this trial, 22% of couples resumed sex early and 25% of the men had not disclosed their HIV status, underscoring the importance of joint couple counselling and testing to learn serostatus and plan abstinence strategies for the healing period.**

Mehta SD, Gray RH, Auvert B, Moses S, Kigozi G, Taljaard D, Puren A, Agot K, Serwadda D, Parker CB, Wawer MJ, Bailey RC. Does sex in the early period after circumcision increase HIV-seroconversion risk? *AIDS*. 2009 Jun 29. [Epub ahead of print]

Mehta et al set out to evaluate whether sexual intercourse soon after adult male circumcision affected HIV risk by conducting a combined analysis of data from African trials of men who were randomized to and underwent circumcision. The authors examined two associations: early sex (intercourse <42 days after circumcision) and HIV acquisition at 3 months for the Orange Farm and Kisumu trials and at 6 months for the Rakai and Kisumu trials and incomplete wound healing at 1 month and seroconversion at 3 and 6 months for the Kisumu trial and at 6 months for the Rakai trial. Early sex was reported by 3.9% of participants in Kisumu, 5.4% in Rakai, and 22.5% in Orange Farm. HIV seroprevalence was 0.0% at 3 months and 1.9% at 6 months among 18-24-year-olds reporting early sex and 0.2% at 3 months and 0.6% at 6 months among those who did not report early sex. In pooled analyses, men reporting early sex did not have higher HIV infection risk at 3 or 6 months. In Kisumu, 16 (1.3%) men had incomplete wound healing at the 30-day visit. One (6.3%) of these seroconverted at 3 months compared with 2 (0.2%) of 1246 men with complete wound healing (P = 0.075). No association was observed between incomplete wound healing and seroconversion for Rakai participants. The authors conclude that most men delayed intercourse after circumcision. Early sex after circumcision was not associated with HIV risk, although the study power was limited. Nevertheless, men should delay intercourse to limit the potential for increased HIV risk until complete wound healing. **Editors' note: In an excellent move, these three trials pooled their data to assess the risk to HIV-negative men of early resumption of sex after circumcision. Slightly different definitions of wound healing (e.g. Rakai: healthy scar formation, no scab or open wound; Kisumu: no scab, open wound, swelling or redness), different follow-up periods, and the low number of seroconversions observed in the 6 months after circumcision limited the power to detect meaningful associations. In all 3 trials, early sex was reported more often among men who were married or living as married. For such men, involving women in decision-making about circumcision would facilitate couple counselling about avoiding sexual intercourse during the healing period and practising safer sex thereafter.**

2. Programme evaluation: equity

Makwiza I, Nyirenda L, Bongololo G, Banda T, Chimzizi R, Theobald S. Who has access to counselling and testing and anti-retroviral therapy in Malawi - an equity analysis. *Int J Equity Health*. 2009;8(1):13.

The HIV epidemic in Malawi poses multiple challenges from an equity perspective. It is estimated that 12% of Malawians are living with HIV among the 15-49 age group. This paper synthesises available information to bring an equity lens on counselling and testing and antiretroviral therapy policy, practice and provision in Malawi. A synthesis of a wide range of published and unpublished reports and studies using a variety of methodological approaches was undertaken. The analysis and recommendations were developed, through consultation with key stakeholders in Malawi. At the policy level Malawi is unique in having an equity in access to antiretroviral therapy policy, and equity considerations are also included in key counselling and testing documents. The number of people accessing counselling and testing has increased considerably from 149,540 in 2002 to 482,364 in 2005. There is urban bias in provision of counselling and testing and more women than men access counselling and testing. Antiretroviral therapy has been provided free since June 2004 and scale up of antiretroviral therapy provision is gathering pace. By end December 2006, there were 85,168 patients who had ever started on antiretroviral therapy in both the public and private health sector, 39% of the patients were male while 61% were female. The majority of patients were adults, and

7% were children, aged 14 years or below. Despite free antiretroviral therapy services, patients, especially poor rural patients, face significant barriers in access and adherence to services. There are missed opportunities in strengthening integration between counselling and testing and antiretroviral therapy and tuberculosis, sexually transmitted infections, and maternal health services. To promote equitable access for counselling and testing and antiretroviral therapy in Malawi there is need to further invest in human resources for health, and seize opportunities to integrate counselling and testing and antiretroviral therapy services with tuberculosis, sexually transmitted infection and maternal health services. This should not only promote access to services but also ensure that resources available for counselling and testing and antiretroviral therapy strengthen rather than undermine the provision of the essential health package in Malawi. Ongoing equity analysis of services is important in analyzing which groups are unrepresented in services and developing initiatives to address these. Creative models of decentralization, whilst maintaining quality of services are needed to further enhance access of poor rural women, men, girls and boys. **Editors' note: Although only 43% of Malawians in need of antiretroviral treatment had accessed it by the end of 2006, Malawi is well on its way to meeting its universal access treatment target of 50%. A clear priority in Malawi has been to promote equity in access to its free treatment first-come first-served programme that has been running since 2004. Significant barriers to achieving equity in access are the cost of transport and food as well as the opportunity costs of missing work, particularly when tuberculosis and antiretroviral treatment programmes are parallel, vertical programmes requiring separate clinic visits. Monitoring the age, sex, and socioeconomic status of people undergoing HIV testing and accessing HIV treatment services in all countries can help identify inequities that are unnecessary, avoidable, and unfair so that they can be rectified.**

Cornell M, Myer L, Kaplan R, Bekker LG, Wood R. The impact of gender and income on survival and retention in a South African antiretroviral therapy programme. *Trop Med Int Health.* 2009 Apr 27. [Epub ahead of print]

Despite the rapid expansion of antiretroviral therapy services in Africa, there are few data on whether outcomes differ for women and men and what factors may drive such variation. Cornell and colleagues investigated the association of gender and income with survival and retention in a South African antiretroviral therapy programme. A total of 2196 treatment-naïve adults were followed for 1 year on antiretroviral therapy. Proportional hazards regression was used to explore associations between baseline characteristics and survival and loss-to-follow-up. Patients were predominantly female (67%). Men presented at an older age and with more advanced HIV disease, and during early antiretroviral therapy the crude death rate was higher among men than women (22.8 vs 12.5/100 person-years; $P = 0.002$). However in multivariate analysis, gender was not significantly associated with survival after adjusting for baseline clinical and immunovirological status (HR = 1.46, 95% CI = 0.96-2.22; $P = 0.076$). In late antiretroviral therapy (4-12 months), there was no gender difference in mortality rates (3.5 vs 3.8/100 person-years; $P = 0.817$). In multivariate analysis, survival was strongly associated with age (HR = 1.05, 95% CI = 1.02-1.09; $P < 0.001$), CD4 count >150 vs <50 cells/mul (HR = 0.35, 95% CI = 0.14-0.87; $P = 0.023$) and any monthly income vs none (HR = 0.47, 95% CI = 0.25-0.88; $P = 0.018$). Having some monthly income was protective against loss-to-follow-up at 1 year on antiretroviral therapy (adjusted HR = 0.56, 95% CI = 0.39-0.82; $P = 0.002$). Men's high early mortality on antiretroviral therapy appears due largely to

their presentation with more advanced HIV disease. Efforts are needed to enrol men into care earlier in HIV disease and to reduce socio-economic inequalities in antiretroviral therapy programme outcomes. **Editors' note: This study provides additional evidence to support the need for strategies to increase men's exposure to health services and decrease their disadvantages in access to HIV testing and treatment in resource-constrained settings. Some of the barriers are psychosocial while others are structural. This study also found that people with no monthly income experience poorer treatment outcomes: Compared to women with no monthly income, men with no monthly income had nearly twice the crude hazard of death. Socioeconomic interventions, such as the proposed basic income grant in South Africa, may improve patient retention and survival in antiretroviral treatment programmes.**

3. Injecting-drug users

Des Jarlais DC, McKnight C, Goldblatt C, Purchase D. Doing harm reduction better: syringe exchange in the United States. *Addiction*. 2009 Feb 10. [Epub ahead of print]

To trace the growth of syringe exchange programs in the United States since 1994-95 and assess the current state of syringe exchange programs, annual surveys of US syringe exchange programs known to the North American Syringe Exchange Network (NASEN) were mailed to executive directors with follow-up interviews by telephone and/or e-mail. Response rates have varied between 70% and 88% since surveys were initiated in 1996. The numbers of programs known to NASEN have increased from 68 in 1994-95 to 186 in 2007. Among programs participating in the survey, numbers of syringes exchanged have increased from 8.0 million per year to 29.5 million per year, total annual budgets have increased from \$6.3 to \$19.6 million and public funding (from state and local governments) has increased from \$3.9 to \$14.4 million. In 2007, 89% of programs permitted secondary exchange and 76% encouraged it. Condoms, referrals to substance abuse treatment; human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV) counselling and testing and naloxone for overdose were among the most commonly provided services in addition to basic syringe exchange. Each of these services was provided by 40% or more of syringe exchange programs in 2007. While syringe exchange has remained controversial in the United States, there has been very substantial growth in numbers of programs, syringes exchange and program budgets. Utilizing secondary exchange to reach large numbers of injecting drug users and utilizing syringe exchange programs as a new platform for providing health and social services beyond basic syringe exchange have been the two major organizational strategies in the growth of syringe exchange programs in the United States. **Editors' note: Two-thirds of these US programmes do not adhere to a restrictive 'one-for-one' needle exchange policy and 89% permit secondary exchange, allowing an individual participant to exchange for peers who do not necessarily attend the exchange. These policies have served to increase the numbers of sterile syringes available to injecting drug users with the result that HIV incidence in the USA has declined to under 1 per 100 person years and the majority of new infections among injecting drug users appear to be sexually transmitted. The recent Congress bill lifting the 20-year ban on federal funding for needle exchange <http://www.speaker.gov/blog/?p=1885> may encourage more equitable service coverage across the US, reduce stigmatisation of drug users, and facilitate a move toward integration of services for drug users into the regular health system.**

4. Paediatric outcomes

Briand N, Mandelbrot L, Le Chenadec J, Tubiana R, Teglas JP, Faye A, Dollfus C, Rouzioux C, Blanche S, Warszawski J; for the ANRS French Perinatal Cohort. No relation between in-utero exposure to HAART and intrauterine growth retardation. *AIDS*. 2009;23(10):1235-43

The use of highly active antiretroviral treatment during pregnancy is now standard care to prevent mother-to-child HIV transmission in developed countries. There is controversy about its impact on low birth weight. Briand and colleagues set out to evaluate the impact of antiretroviral therapy during the pregnancy on birth weight, length, and head circumference. The study was performed in uninfected infants born to HIV-1-infected mothers, enrolled from 1990 to 2006 in the Agence Nationale de Recherches sur le SIDA French Perinatal Cohort CO1. The authors excluded mothers who used illicit drugs during pregnancy or had no prenatal care before the third trimester, twins and stillbirths. They used Z-scores adjusted for gestational age and sex. In 8192 mother-infant pairs, the mean birth weight Z-scores increased between 1990 and 1997 and then remained stable until 2006. There was no significant relation between the type of antiretroviral therapy and the proportion of small for gestational age (birth weight Z-score $\leq -2SD$), which was 4% overall. Infants exposed to highly active antiretroviral treatment compared with mono antiretroviral therapy had a lower mean birth weight Z-scores (difference -0.09, 95% confidence interval -0.15 to -0.02); however, there was no difference between highly active antiretroviral treatment exposure in 2005-2006 and monotherapy in 1999-2004, which corresponded to standard care during each period, respectively. Length or head circumference Z-scores were not associated with antiretroviral therapy exposure. Among pregnancies with highly active antiretroviral treatment, there was no relation between the duration and type of therapy and the anthropometric parameters. Those findings in a large cohort suggest that highly active antiretroviral treatment during pregnancy does not increase the incidence of infants who are small for gestational age. **Editors' note: Z-scores are standard scores based on the normal distribution and in this case are French standards. In this study, uninfected infants were judged small for gestational age if their birth weight Z-score was lower than 2 standard deviations, corresponding to the third percentile adjusted for gestational age and sex. Since 2004, combination antiretroviral treatment has been recommended for all HIV-positive pregnant women in France and, in 2005-2006, 93% of women in the 90 centres of the cohort received it to prevent mother-to-child transmission. Encouragingly, increasing use of antiretroviral drugs during pregnancy in France over the past 15 years has not increased the incidence of small for gestational age infants, nor affected length or head circumference.**

Smith K, Kuhn L, Coovadia A, Meyers T, Hu CC, Reitz C, Barry G, Strehlau R, Sherman G, Abrams EJ. Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. *AIDS*. 2009;23(9):1097-107.

Smith and colleagues set out to determine the incidence, clinical manifestations, and risk factors for immune reconstitution inflammatory syndrome (IRIS) in young children initiating highly active antiretroviral therapy. Using data from a prospective cohort of antiretroviral-naïve HIV-infected children less than 24 months of age enrolled in a treatment strategies trial in Johannesburg, South Africa. Among 169 HIV-infected children initiating antiretroviral therapy, April 2005 to November 2006, the records of 83 children suspected to have IRIS within 6 months of starting treatment were reviewed to determine whether they met criteria for IRIS. Seven were excluded due to incomplete follow-up. Pretreatment and post-treatment characteristics of children with and without IRIS were compared. Overall, 34/162 (21%) children developed IRIS at a median of 16 days (range 7-115 days) post-antiretroviral therapy initiation. Bacille Calmette-Guérin reaction was most common occurring in 24/34 (71%) children, primarily injection site lesions and/or ipsilateral axillary

lymphadenitis with abscess. Other IRIS conditions (not mutually exclusive) included Mycobacterium tuberculosis (n = 12), cytomegalovirus pneumonia (n = 1), Streptococcus pneumonia sepsis (n = 1), and severe seborrheic dermatitis (n = 1). Children with IRIS were younger (median age 7 vs. 10 months, P = 0.007) with a lower CD4 cell percentage (median 13.9 vs. 19.2, P = 0.009) at antiretroviral treatment initiation than controls. After 24 weeks on antiretroviral treatment, 62% of IRIS cases vs. 28% of controls had HIV RNA more than 400 copies/ml (P = 0.001), odds ratio = 2.88 (95% confidence interval = 1.14-7.29) after adjusting for baseline factors. Infants and young children with advanced HIV disease initiating antiretroviral treatment are at high risk for developing IRIS, leading to additional morbidity and possibly impairing virologic response to antiretroviral treatment. **Editors' note: All the children in this study had advanced HIV disease at the time of antiretroviral treatment initiation so it is possible that the incidence of immune reconstitution inflammatory syndrome (IRIS) would be much lower when infants are started on treatment as soon as they are diagnosed, as is currently recommended. The fact that the most common IRIS manifestation in this study (71% of children) was reaction to the tuberculosis vaccine BCG lends support to the WHO guidelines discouraging BCG for HIV-infected infants.**

Hesseling AC, Johnson LF, Jaspan H, Cotton MF, Whitelaw A, Schaaf HS, Fine PEM, Eley BS, Marais BJ, Nuttall J, Beyersa N, Godfrey-Faussettg P. Disseminated bacille Calmette-Guérin disease in HIV-infected South African infants. *Bull World Health Organ.* 2009;87:505-511.

The authors set out to determine the population-based incidence of disseminated bacille Calmette-Guérin (BCG) disease in HIV-infected infants (aged less than 1 year) in a setting with a high burden of tuberculosis and HIV infection coupled with a well-functioning programme for the prevention of HIV infection in infants. The numerator, or number of new cases of disseminated BCG disease, was derived from multicentre surveillance data collected prospectively on infants with a confirmed HIV infection during 2004-2006. The denominator, or total number of HIV-infected infants who were BCG-vaccinated, was derived from population-based estimates of the number of live infants and from reported maternal HIV infection prevalence, vertical HIV transmission rates and BCG vaccination rates. The estimated incidences of disseminated BCG disease per 100 000 BCG-vaccinated, HIV-infected infants were as follows: 778 (95% confidence interval, CI: 361-1319) in 2004 (vertical HIV transmission rate: 10.4%); 1300 (95% CI: 587-2290) in 2005 (transmission rate: 6.1%); and 1013 (95% CI: 377-1895) in 2006 (transmission rate: 5.4%). The pooled incidence over the study period was 992 (95% CI: 567-1495) per 100 000. Multicentre surveillance data showed that the risk of disseminated BCG disease in HIV-infected infants is considerably higher than previously estimated, although likely to be under-estimated. There is an urgent need for data on the risk-benefit ratio of BCG vaccination in HIV-infected infants to inform decision-making in settings where HIV infection and tuberculosis burdens are high. Safe and effective tuberculosis prevention strategies are needed for HIV-infected infants. **Editors' note: In light of the results of this three-year multicentre surveillance study in South Africa, WHO now recommends that BCG vaccination be delayed for all babies born to mothers with HIV infection until they are determined to not have HIV infection, even in high TB burden settings. This gives added impetus to UNAIDS' call at the 2009 World Health Assembly for the elimination of mother-to-child transmission by 2015. Strengthened antenatal services, increased HIV testing uptake, contraceptive services for women living with HIV who are not planning a**

pregnancy, timely provision of antiretroviral prophylaxis, and infant feeding counselling are among the building blocks to achieve this goal.

5. Health care delivery

Price JE, Leslie JA, Welsh M, Binagwaho A. Integrating HIV clinical services into primary health care in Rwanda: a measure of quantitative effects. *AIDS Care*. 2009;21(5):608-14.

With the intensive scale-up of care and treatment for HIV in developing countries, some fear that intensified attention to HIV programmes may overwhelm health care systems and lead to declines in delivery of other primary health care. Few data exist that confirm negative or positive synergies on health care provision generally resulting from HIV-dedicated programs. Using a retrospective observational design Price and colleagues compare aggregate service data in Rwandan health facilities before and after the introduction of HIV care on selected measures of primary health care. The study tests the hypothesis that non-HIV care does not decrease after the introduction of basic HIV care. Overall, no declines were observed in reproductive health services, services for children, laboratory tests, and curative care. Statistically significant increases were found in utilization and provision of some preventive services. Multivariate regression, including introduction of HIV care and two important health care financing initiatives in Rwanda, revealed positive associations of all with observed increases. Introduction of HIV services was especially associated with increases in reproductive health. While hospitalization rates increased for the whole sample, declines were observed at health facilities that offered basic HIV care plus highly active antiretroviral therapy. The authors indicate that their results partially counter fears that HIV programs are producing adverse effects in non-HIV service delivery. Rather than leading to declines in other primary health care delivery, they say their findings suggest that the integration of HIV clinical services may contribute to increases. **Editors' note: This study of 30 primary health centres that had at least 6 months experience offering basic HIV care, defined as voluntary counselling and testing, prevention of mother-to-child transmission services, and preventive therapy with cotrimoxazole, found positive synergies between HIV care and the delivery of other primary care services, particularly antenatal care. This study would be strengthened by consideration of outcome indicators, such as maternal mortality and incidence of congenital syphilis, rather than solely service utilisation indicators. The changes documented here occurred against a backdrop of two important nationally coordinated health care financing programmes that the researchers did try to take into account- the *mutuelle de santé*, Rwanda's nationwide primary health insurance system, and performance based financing of health centres. Both of these programmes would be expected to increase uptake and improve outcomes.**

Hanefeld J, Musheke M. What impact do Global Health Initiatives have on human resources for antiretroviral treatment roll-out? A qualitative policy analysis of implementation processes in Zambia. *Hum Resour Health*. 2009 Feb 10;7(1):8. [Epub ahead of print]

Since the beginning of the 21st century, development assistance for AIDS has increasingly been provided through Global Health Initiatives (GHI), specifically the United States Presidential Emergency Plan for AIDS Relief, the Global Fund to Fight HIV, TB and Malaria and the World Bank Multi-country AIDS Programme. Zambia, like many of the countries heavily affected by HIV in southern Africa, also faces a shortage of human resources for health. The country receives significant amounts of funding from GHIs for the large-scale

provision of antiretroviral treatment through the public and private sector. This paper examines the impact of GHIs on human resources for antiretroviral treatment roll-out in Zambia, at national level, in one province and two districts. Hanefeld and Musheke undertook a qualitative policy analysis relying on in-depth interviews with more than 90 policy-makers and implementers at all levels. Findings show that while GHIs do not provide significant funding for additional human resources, their interventions have significant impact on human resources for health at all levels. While GHIs successfully retrain a large number of health workers, evidence suggests that GHIs actively deplete the pool of skilled human resources for health by recruiting public sector staff to work for GHI-funded nongovernmental implementing agencies. The secondment of GHI staff into public sector facilities may help alleviate immediate staff shortages, but this practice risks undermining sustainability of programmes. GHI-supported programmes and initiatives add significantly to the workload of existing public sector staff at all levels, while incentives including salary top-ups and overtime payments mean that antiretroviral treatment programmes are more popular among staff than services for non-focal diseases. Research findings suggest that GHIs need to actively mediate against the potentially negative consequences of their funding on human resources for health. Evidence presented highlights the need for new strategies that integrate retraining of existing staff with longer-term staff development to ensure staff retention. The study results show that GHIs must provide significant new and longer-term funding for additional human resources to avoid negative consequences on the overall provision of health care services and to ensure sustainability and quality of programmes they support. **Editors' note: Zambia faces a severe shortage in human resources for health with the greatest need being for laboratory technicians, followed by pharmacists, doctors, nurses, and data monitors. There is rapid turnover of staff, high staff absenteeism, and unequal urban-rural distribution. At the time this research was conducted, the only targeted human resource intervention receiving any donor support was the rural retention scheme. Countries should require Global Health Initiatives to conduct human resource impact assessments. It is time to think seriously about the wisdom of addressing public sector human resources needs, in the interest of the long-term sustainability of antiretroviral treatment programmes.**

6. *People living with HIV*

Kimbrough LW, Fisher HH, Jones KT, Johnson WD, Thadiparthi S, Dooley S. Centers for Disease Control and Prevention. Accessing Social Networks With High Rates of Undiagnosed HIV Infection: The Social Networks Demonstration Project. *Am J Public Health*. 2009;99(6):1093-9.

Kimbrough and colleagues evaluated the use of social networks to reach persons with undiagnosed HIV infection in ethnic minority communities and link them to medical care and HIV prevention services. Nine community-based organizations in 7 cities received funding from the United States Centers for Disease Control and Prevention to enlist HIV-positive persons to refer others from their social, sexual, or drug-using networks for HIV testing; to provide HIV counselling, testing, and referral services; and to link HIV-positive and high-risk HIV-negative persons to appropriate medical care and prevention services. From October 1, 2003, to December 31, 2005, 422 recruiters referred 3172 of their peers for HIV services, of whom 177 were determined to be HIV positive; 63% of those who were HIV-positive were successfully linked to medical care and prevention services. The HIV prevalence of 5.6% among those recruited in this project was significantly higher than the approximately 1% identified in other counselling, testing, and referral sites funded by the Centers for Disease

Control and Prevention. This peer-driven approach is highly effective and can help programs identify persons with undiagnosed HIV infection in high-risk networks. **Editors' note: HIV takes advantages of networks so why can't HIV prevention and treatment take advantage of social networks? This peer-driven strategy though community-based organisations proved to be an efficient high-yield approach to accessing and providing HIV counselling, testing, and referral services to key populations at higher risk of HIV exposure that are difficult to reach with other more conventional strategies.**

7. Treatment

Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C, Hogg E, Komarow L. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS ONE*. 2009;4(5):e5575.

Optimal timing of antiretroviral therapy initiation for individuals presenting with AIDS-related opportunistic infections has not been defined. A5164 was a randomized strategy trial of "early antiretroviral therapy"—given within 14 days of starting treatment for acute opportunistic infection versus "deferred antiretroviral therapy"—given after treatment for acute opportunistic infection is completed. Randomization was stratified by presenting opportunistic infections and entry CD4 count. The primary week 48 endpoint was 3-level ordered categorical variable: 1. Death/AIDS progression; 2. No progression with incomplete viral suppression (ie HIV viral load (VL) ≥ 50 copies/ml); 3. No progression with optimal viral suppression (ie HIV VL < 50 copies/ml). Secondary endpoints included: AIDS progression/death; plasma HIV RNA and CD4 responses and safety parameters including IRIS. 282 subjects were evaluable; 141 per arm. Entry opportunistic infections included *Pneumocystis jirovecii* pneumonia 63%, cryptococcal meningitis 12%, and bacterial infections 12%. The early and deferred arms started antiretroviral therapy a median of 12 and 45 days after the start of treatment for opportunistic infections, respectively. AIDS progression/death was seen in 20 (14%) vs. 34 (24%); whereas no progression but with incomplete viral suppression was seen in 54 (38%) vs. 44 (31%); and no progression with optimal viral suppression in 67 (48%) vs 63 (45%) in the early vs. deferred arm, respectively ($p = 0.22$). However, the early antiretroviral therapy arm had fewer AIDS progression/deaths (OR = 0.51; 95% CI = 0.27-0.94) and a longer time to AIDS progression/death (stratified HR = 0.53; 95% CI = 0.30-0.92). The early antiretroviral therapy had shorter time to achieving a CD4 count above 50 cells/mL ($p < 0.001$) and no increase in adverse events. Early antiretroviral therapy resulted in less AIDS progression/death with no increase in adverse events or loss of virologic response compared to deferred antiretroviral therapy. These results support the early initiation of antiretroviral therapy in patients presenting with acute AIDS-related opportunistic infections, absent major contraindications. **Editors' note: Waiting to complete treatment for an opportunistic infection before initiating antiretroviral treatment in this USA/South Africa study was associated with a higher risk of HIV disease progression and/or death, with no safety or virological advantage. Concerns about toxicity, drug-drug interactions, immune reconstitution inflammatory syndrome, and adherence have made clinicians cautious about initiating antiretroviral treatment during treatment for opportunistic infections. However, as this study demonstrates, earlier antiretroviral treatment brings earlier improvement in immune responsiveness, which narrows the 'window of vulnerability' to additional HIV-related complications, preventing clinical progression.**

Demeter LM, Jiang H, Mukherjee AL, Morse GD, Difrancesco R, Dicenzo R, Dykes C, Sista P, Bacheler L, Klingman K, Rinehart A, Albrecht M. A randomized trial of therapeutic drug monitoring of protease inhibitors in antiretroviral-experienced, HIV-1-infected patients. *AIDS*. 2009;23(3):357-68

Whether therapeutic drug monitoring of protease inhibitors improves outcomes in HIV-infected patients is controversial. Demeter and colleagues evaluated this strategy in a randomized, open-label clinical trial, using a normalized inhibitory quotient (NIQ), which incorporates drug exposure and viral drug resistance. NIQs ≤ 1 may predict poor outcome and identify patients who could benefit from dose escalation. Eligible patients had a viral load ≥ 1000 copies/ml on a failing regimen, and began a new protease inhibitor containing regimen at entry. All FDA-approved protease inhibitors available during the study recruitment (June 2002-May 2006) were allowed. One hundred and eighty-three participants with NIQ ≤ 1 , on the basis of their week 2 protease inhibitor trough concentration and pre-entry drug resistance test, were randomized at week 4 to standard of care (SOC) or protease inhibitor dose escalation (therapeutic drug monitoring). The primary endpoint was change in log₁₀ plasma HIV-1 RNA concentration from randomization to 20 weeks later. Ninety-one patients were randomized to standard of care and 92 to therapeutic drug monitoring. NIQs increased more in the therapeutic drug monitoring arm compared to standard of care (+69 versus +25%, P = 0.01). Despite this, therapeutic drug monitoring and standard of care arms showed no difference in outcome (+0.09 versus +0.02 log₁₀, P = 0.17). In retrospective subgroup analyses, patients with less HIV resistance to their protease inhibitors benefited from therapeutic drug monitoring (P = 0.002), as did black and Hispanic patients (P = 0.035 and 0.05, respectively). Differences between black and white patients persisted when accounting for protease inhibitor susceptibility. There was no overall benefit of therapeutic drug monitoring. In post hoc subgroup analyses, therapeutic drug monitoring appeared beneficial in black and Hispanic patients, and in patients whose virus retained some susceptibility to the protease inhibitors in their regimen. **Editors' note: Although the authors state that they compared differences between the therapeutic drug monitoring group and the standard of care group with respect to the primary endpoint (change in viral load after 20 weeks) in specific sub-groups of patients according to sex, race and ethnicity, number of protease inhibitors in the study regimen, and whether fosamprenavir was used) no data are provided for women who constituted 13% of the study participants. This is another example of the 'fugitive data issue' that the Women and Trials movement has identified as problematic. Authors need to make an extra effort to publish these data, as not enough is known about sex differences in pharmacokinetics and pharmacodynamics.**

8. Reproductive health

Stringer EM, Levy J, Sinkala M, Chi BH, Matongo I, Chintu N, Stringer JS. HIV disease progression by hormonal contraceptive method: secondary analysis of a randomized trial. *AIDS*. 2009;23(11):1377-82 14.

HIV-infected women need access to safe contraception. Stringer and colleagues hypothesized that women using depot medroxyprogesterone acetate (DMPA) contraception would have faster HIV disease progression than women using oral contraceptive pills and nonhormonal methods. In a previously reported trial, the authors randomized 599 HIV-infected women to the intrauterine device (IUD) or hormonal contraception. Women randomized to hormonal contraception chose between oral contraceptive pills and DMPA. This

analysis investigates the relationship between exposure to hormonal contraception and HIV disease progression [defined as death, becoming eligible for antiretroviral therapy, or both]. Of the 595 women not on antiretroviral therapy at the time of randomization, 302 were allocated to hormonal contraception, of whom 190 (63%) initiated DMPA and 112 (37%) initiated oral contraceptive pills. Women starting IUD, oral contraceptive pills, or DMPA were similar at baseline. Compared with women using the IUD, the adjusted hazard of death was not significantly increased among women using oral contraceptive pills [1.24; 95% confidence interval (CI) 0.42-3.63] or DMPA (1.83; 95% CI 0.82-4.08). However, women using oral contraceptive pills (adjusted hazard ratio (AHR) 1.69; 95% CI 1.09-2.64) or DMPA (AHR 1.56; 95% CI 1.08-2.26) trended toward an increased likelihood of becoming eligible for antiretroviral therapy. Women exposed to oral contraceptive pills (AHR 1.67; 95% CI 1.10-2.51) and DMPA (AHR 1.62; 95% CI 1.16-2.28) also had an increased hazard of meeting this study's composite disease progression outcome (death or becoming antiretroviral therapy eligible) than women using the IUD. In this secondary analysis, exposure to oral contraceptive pills or DMPA was associated with HIV disease progression among women not yet on antiretroviral therapy. This finding, if confirmed elsewhere, would have global implications and requires urgent further investigation. **Editors' note: The relationship between hormonal contraception and disease progression was not an *a priori* hypothesis of this trial and 47% of the participants switched contraceptive methods, withdrew from the study, or were lost to follow-up. The researchers addressed the switching by treating contraceptive method as a time-varying exposure but the fact that women assigned to the contraceptive arm could choose either DMPA or oral contraceptives could have introduced confounding. Given that the risk of maternal mortality increases with each subsequent pregnancy, with a women's lifetime risk of dying in pregnancy as high as one in 22 in sub-Saharan Africa, women need safe and effective contraception when they want it. These results are by no mean definitive but they support the urgent call for a trial evaluating the potential relationship between HIV disease progression and hormonal contraception.**

9. Basic science

Grabar S, Selinger-Leneman H, Abgrall S, Pialoux G, Weiss L, Costagliola D. Prevalence and comparative characteristics of long-term nonprogressors and HIV controller patients in the French Hospital Database on HIV. *AIDS*. 2009;23(9):1163-9.

Grabar and colleagues set out to estimate the prevalence and characteristics of long-term nonprogressor and HIV controller patients in a very large French cohort of HIV 1-infected patients. In the French Hospital Database on HIV [FHDH, Agence Nationale de Recherches sur le SIDA et les hépatites virales (ANRS) CO4], they selected patients who had been seen in 2005, who had been infected for more than 8 years, who were treatment-naive, and who remained asymptomatic. Patients with these characteristics then categorized as follows: long-term nonprogressor (> or =8 years of HIV infection and CD4 cell nadir > or =500/microl), elite long-term nonprogressor (> or =8 years of HIV infection, CD4 cell nadir > or =600/microl, and a positive CD4 slope), HIV controllers (>10 years of HIV infection with 90% of plasma viral load values < or =500 copies/ml), and elite controllers (same as HIV controllers, but with last plasma viral load value < or =50 copies/ml in 2005). Among the 46 880 HIV-1-infected patients followed in 2005 in the French Hospital Database on HIV, 0.4% (N = 202) were long-term nonprogressor, 0.05% (N = 25) were elite long-term nonprogressor, 0.22% (N = 101) were HIV controllers, and 0.15% (N = 69) were elite controllers. Ten elite

long-term nonprogressor patients (40% of 25) were also HIV controllers, eight (32%) were elite controllers, and 60% had detectable plasma viral load (>50 copies/ml). Among the elite controllers, 32 (46%) were long-term nonprogressor, eight (12%) were elite long-term nonprogressor, and one-quarter had a last CD4 cell count less than 500/microl. Long-term nonprogressor, elite LTNP, HIV controller, and elite controller patients are rare phenotypes. Elite long-term nonprogressor patients are less frequent than HIV controllers. There is little overlap among the four subgroups of patients. **Editors' note: With the advent of viral load assays in clinical care, new groups of patients with slow disease progression joined the patients known as long-term nonprogressors. Defined by virologic parameters, they are called the HIV controllers, some of whom are elite controllers. Although the definitions of these various groups vary in the literature and there is some overlap, they are of intense interest because the mechanisms by which they have some natural protection against HIV may provide insights for the development of preventive and therapeutic vaccines. Both viral factors and host genetic factors, such as HLA-B27 and HLA-B57, may play a role. This study of more than 110,000 patients confirms the very low prevalence (less than 0.5%) of these valuable patients. Some are viraemic with high CD4 counts while others control viraemia but have CD4 depletion and yet others appear to have both viral control and stable CD4 cell counts.**

Lassen KG, Lobritz MA, Bailey JR, Johnston S, Nguyen S, Lee B, Chou T, Siliciano RF, Markowitz M, Arts EJ. Elite suppressor-derived HIV-1 envelope glycoproteins exhibit reduced entry efficiency and kinetics. *PLoS Pathog.* 2009;5(4):e1000377.

Elite suppressors are a rare subset of HIV-1-infected individuals who are able to maintain HIV-1 viral loads below the limit of detection by ultra-sensitive clinical assays in the absence of antiretroviral therapy. Mechanism(s) responsible for this elite control are poorly understood but likely involve both host and viral factors. This study assesses elite suppressors plasma-derived envelope glycoprotein (env) fitness as a function of entry efficiency as a possible contributor to viral suppression. Fitness of virus entry was first evaluated using a novel inducible cell line with controlled surface expression levels of CD4 (receptor) and CCR5 (co-receptor). In the context of physiologic CCR5 and CD4 surface densities, elite suppressors envs exhibited significantly decreased entry efficiency relative to chronically infected viremic progressors. Elite suppressors envs also demonstrated slow entry kinetics indicating the presence of virus with reduced entry fitness. Overall, elite suppressors env clones were less efficient at mediating entry than chronic progressor envs. Interestingly, acute infection envs exhibited an intermediate phenotypic pattern not distinctly different from elite suppressors or chronic progressor envs. These results imply that lower env fitness may be established early and may directly contribute to viral suppression in elite suppressors individuals. **Editors' note: This study is the first to provide direct evidence that the envelope glycoprotein, the coat protein of HIV, in elite suppressors is less efficient in supporting HIV entry into host cells than that of HIV found in people with disease progression. In acute infection, there are HIV variants with a wide range of efficiencies, suggesting that elite suppressors may be selecting relatively lower fitness env variants right at the start. How they would do this remains a mystery, as no data exist on the natural history of acute infection in elite suppressors.**

10. Resistance

Van de Vijver DA, Derdelinckx I, Boucher CA. Department of Virology, Erasmus MC, University Medical Centre Rotterdam, and 2Department of Medical Microbiology, University Medical Centre Utrecht, the Netherlands. Circulating HIV type 1 drug resistance will have limited impact on the effectiveness of preexposure prophylaxis among young women in Zimbabwe. *J Infect Dis.* 2009;199(9):1310-7.

Preexposure prophylaxis (PrEP) with antiretroviral drugs may prevent transmission of human immunodeficiency virus (HIV). The objective of van de Vijver and colleagues was to predict whether PrEP, in the presence of circulating drug resistance, will reduce the risk of infection with HIV. They used risk equations to calculate the monthly risk of infection with HIV before and after the introduction of PrEP. Uncertainty and sensitivity analyses were performed for 2 ranges of PrEP effectiveness (40%-60% and 60%-80%). Circulating drug resistance was assumed to reduce the effectiveness of PrEP by 50%-90% and the transmissibility of HIV by 0%-30%. Parameter ranges were chosen for women 17-29 years of age from publications on HIV in Manicaland in Zimbabwe. PrEP would decrease the median risk of HIV transmission by 21%-33% (effectiveness of PrEP, 40%-60% and 60%-80%). If 50% of HIV strains are drug resistant, then the median risk reduction would be 19%-26% if drug-resistant strains were less transmissible than wild-type HIV and 12%-19% if they were equally transmissible. The risk would increase if condoms were frequently replaced with PrEP. Use of PrEP for sexual acts for which no protection is currently used would be beneficial. The public health impact of PrEP will depend on its effectiveness and on risk behaviour. Circulating drug resistance will have only a small impact on the effectiveness of PrEP. **Editors' note: As this mathematical modelling shows, the precise impact of PrEP will depend on many factors such as its effectiveness (which remains to be determined by clinical trials in humans), the prevalence of condom use, the frequency with which condom use is replaced by PrEP when it becomes available, the number of sex acts performed, and the level of PrEP use among individuals currently not using condoms. Most discussion of drug resistance in relation to PrEP has focused on the extent to which PrEP use might create drug resistance. Interestingly, this model looked at the impact on PrEP of various levels of circulating M184V, the mutation resistant to emtricitabine or FTC. The model predicts limited impact of population-level drug resistance on PrEP's contribution to HIV prevention, assuming that resistant virus is less fit.**

Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, Kiuchi M, Heneine W, Kantor R, Jordan MR, Schapiro JM, Vandamme AM, Sandstrom P, Boucher CA, van de Vijver D, Rhee SY, Liu TF, Pillay D, Shafer RW. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. *PLoS ONE.* 2009;4(3):e4724.

Programs that monitor local, national, and regional levels of transmitted HIV-1 drug resistance inform treatment guidelines and provide feedback on the success of HIV-1 treatment and prevention programs. To accurately compare transmitted drug resistance rates across geographic regions and times, the World Health Organization has recommended the adoption of a consensus genotypic definition of transmitted HIV-1 drug resistance. In January 2007, Bennet and colleagues outlined criteria for developing a list of mutations for drug-resistance surveillance and compiled a list of 80 reverse transcriptase and protease mutations meeting these criteria (surveillance drug resistance mutations). Since January 2007, several new drugs have been approved and several new drug-resistance mutations have been identified. In this paper, the authors follow the same procedures described previously

to develop an updated list of surveillance drug resistance mutations that are likely to be useful for ongoing and future studies of transmitted drug resistance. The updated surveillance drug resistance mutation list has 93 mutations including 34 non-nucleoside reverse transcriptase protease inhibitor-resistance mutations at 15 reverse transcriptase positions, 19 non-nucleoside reverse transcriptase protease inhibitor-resistance mutations at 10 reverse transcriptase positions, and 40 protease inhibitor-resistance mutations at 18 protease positions. **Editors' note: Population-based surveillance of transmitted drug resistance in recently infected individuals is a cornerstone of optimal treatment programmes. This WHO updated list of surveillance drug mutations is not designed to be used for individual patient management. Rather, its value lies in the fact that it permits accurate estimation of transmitted resistance as well as comparison of estimates of transmitted resistance from different regions and times.**

11. Sexual behaviour

Todd J, Cremin I, McGrath N, Bwanika JB, Wringe A, Marston M, Kasamba I, Mushati P, Lutalo T, Hosegood V, Zaba B. Reported number of sexual partners: comparison of data from four African longitudinal studies. *Sex Transm Infect.* 2009 Apr;85 Suppl 1:i72-80.

Todd et al set out to compare reported numbers of sexual partners in Eastern and Southern Africa. Sexual partnership data from four longitudinal population-based surveys (1998-2007) in Zimbabwe, Uganda and South Africa were aggregated and overall proportions reporting more than one lifetime sexual partner calculated. A lexis-style table was used to illustrate the average lifetime sexual partners by site, sex, age group and birth cohort. The male-to-female ratio of mean number of partnerships in the last 12 months was calculated by site and survey. For each single year of age, the proportion sexually active in the past year, the mean number of partners in the past year and the proportion with more than one partner in the past year were calculated. Over 90% of men and women between 25 and 45 years of age reported being sexually active during the past 12 months, with most reporting at least one sexual partner. Overall, men reported higher numbers of lifetime sexual partners and partners in the last year than women. The male-to-female ratio of mean partnerships in the last year ranged from 1.41 to 1.86. In southern African cohorts, individuals in later birth cohorts reported fewer sexual partners and a lower proportion reported multiple partnerships compared with earlier birth cohorts, whereas these behavioural changes were not observed in the Ugandan cohorts. Across the four sites, reports of sexual partnerships followed a similar pattern for each sex. The longitudinal results show that reductions in the number of partnerships were more evident in southern Africa than in Uganda.

Editors' note: This interesting analysis compares sexual behaviour trends over time in four sites in East and Southern Africa, finding decreased numbers of lifetime sexual partners reported by later birth cohorts. The exception is Uganda, where this change has been described as occurring in the 1990s before the period considered in this paper. Despite different levels of HIV prevalence, the reported number of sexual partners is similar across these four sites. Qualitative research would help interpret these findings and explore the suggestion that differences in partner types and partnership duration may help explain the observed discrepancies in HIV prevalence.

12. Research financing

Moran M, Guzman J, Ropars AL, McDonald A, Jameson N, Omune B, Ryan S, Wu L. Neglected disease research and development: how much are we really spending? *PLoS Med.* 2009;6(2):e30.

The need for new pharmaceutical tools to prevent and treat neglected diseases is widely accepted. However, funders wishing to invest in this vitally important area currently face an information gap. In order to address these information deficits, the Bill & Melinda Gates Foundation commissioned the George Institute for International Health to conduct five sequential annual surveys of global investment into research and development (R&D) of new pharmaceutical products to prevent, manage, or cure diseases of the developing world. This article summarises key data from the first G-FINDER report. G-FINDER was designed to include all neglected diseases and products of significance to developing countries, seeking to capture 2007 data from more than 500 funders and countries. Just over US\$2.5 billion was invested into R&D of new neglected disease products in 2007. Funding was highly concentrated, with AIDS, TB, and malaria receiving nearly 80% of the total. Overall, product R&D investment was heavily focused on drugs and vaccines. Investment in new diagnostics was patchy, while platform technologies applicable to many diseases, for instance vaccine adjuvants, diagnostic platforms, and delivery technologies, received less than 0.4% of total R&D investment. Neglected disease funding remains primarily the realm of public and philanthropic donors, who collectively invested US\$2.3 billion or 90% of the total funding in 2007. Several major OECD (Organisation for Economic Co-operation and Development) governments were missing in action from the top 10, top 20, or even the top 50 funders of R&D for neglected diseases. It is also remarkable that investment by some private firms is now rivalling or exceeding spending by many public organizations. While the authors commend these companies and philanthropists, their efforts are meant to support, not replace, those of wealthy governments around the world. A broadening of funding efforts so that all who are able to contribute do so, and all diseases receive the attention they deserve, would lead to a dramatic positive impact on the health of developing country patients afflicted with these diseases. **Editors' note: Neglected diseases were defined in this survey research as diseases that disproportionately affect people in developing countries for which there is a need for new products and for which there is market failure, i.e. there is no commercial market to attract research and development by private industry. This survey, which included a wide range of funders and countries, found little correlation between research funding and burden of disease, as measure by disability-adjusted life years (DALYs). This suggests that beyond scientific and epidemiological considerations, investment decisions may be influenced by donor perceptions and preferences, the presence of policy frameworks and funding mechanisms that prioritise specific diseases, the possibility of product development partnerships, and the influence of civil society advocacy. However, the overall pie is too small for the task and it is clearly time for those who can contribute to step forward now.**

That was *HIV this week*, signing off.

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