Welcome to the 70th issue of *HIV This Week!* In this issue, we cover **HIV testing** (why pregnant women need extra protection in pregnancy; home-based HIV testing and counselling on Likoma Island, Malawi increases access to prevention and treatment for the poorest households), **pathogenesis and prognosis** (African descent predicts slower CD4 cell count decline in Switzerland; did the advent of combination antiretroviral treatment in 1996 abort increasing HIV virulence?), **structural determinants: prison** (88 seroconversions in prisons in Georgia, USA provoke reflection), **cost-effectiveness** (a 7-country study shows that human resources are the major impediment to reducing incidence of HIV infection in infants by 50% by 2010; the decision-makers' programme planning tool determines costs and the potential impact of male circumcision on Botswana's HIV epidemic), **health information systems** (why PMTCT programme data collection has to improve clinical practice locally first in order for national data to be valid), **monitoring and evaluation** (how well PEPFAR did in Africa from 2004 to 2007), **national responses: policy** (policy analysis shows a way forward in Pakistan), **sexual behaviour** (heterosexual anal intercourse in Cape Town, South Africa), **epidemiology** (how mortality in people living with HIV compares to that of the general population in sub-Saharan Africa), **cardiovascular morbidity and HIV** (atherosclerosis and HIV infection: the carotid reveals a link; HIV infection increases plasma proteins that are associated with risk of heart attack), **trial conduct** (people who inject drugs in Sydney, Australia reveal challenges for vaccine trial recruitment), and **girls and sexual violence** (one-third of Swazi girls experience sexual violence before they turn 18 years old).

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1. **HIV Testing**
The objective of this study was to determine the incidence of HIV during pregnancy as defined by seroconversion using a repeat HIV rapid testing strategy during late pregnancy. In this cross-sectional study nested in a prevention of mother-to-child transmission program, pregnant women were retested between 36 and 40 weeks of gestation, provided that they had been tested HIV negative at least 3 months prior. Among the 2377 HIV-negative women retested, 1099 (46.2%) and 1278 (53.4%) were tested at urban and rural health facilities, respectively. Seventy-two women (3%) were HIV-positive (679 woman years of exposure) yielding a HIV incidence rate of 10.7/100 woman years [95% confidence interval (CI) 8.2-13.1]. HIV incidence in pregnancy was higher but not statistically significant at the urban facilities (12.4/100 woman years versus 9.1/100 woman years) and at least two-fold higher among the 25-29 and 30-34-year age groups (3.8 and 4.5%, respectively) as compared with the less than 20-year age group (1.9%). Single women were at 2.5 times higher risk of seroconverting during pregnancy (P = 0.017). HIV incidence during pregnancy was four times higher than in the non-pregnant population reported in a recent survey. Public health programs need to continue to reinforce prevention strategies and HIV retesting during pregnancy. The latter also offers an additional opportunity to prevent mother-to-child transmission and further horizontal transmission. Further research is required to understand the cause of primary HIV infection in pregnancy. Editors' note: Condom use, multiple sex partners, and the frequency of sexual activity were not significantly different between HIV-negative and seroconverting women in this study, giving support to the idea that hormonal changes affecting either genital mucosa or immune responses may be key. The striking HIV incidence of 10.7 per 100 woman-years underscores the importance of counselling and community education about HIV prevention in pregnancy, as has been done for cigarette smoking and alcohol, to protect pregnant women. Repeat HIV testing offers an additional opportunity to prevent mother-to-child and sexual transmission, along with clinical assessment and care for women who seroconvert.


Uptake of HIV testing and counselling is lower among members of the poorest households in sub-Saharan countries, thereby creating significant inequalities in access to HIV testing and counselling and possibly antiretroviral treatment. Helleringer and colleagues set out to measure uptake of home-based HIV testing and counselling and estimate HIV prevalence among members of the poorest households in a sub-Saharan population. Residents of 6 villages of Likoma Island (Malawi) aged 18-35 and their spouses were offered home-based HIV testing and counselling services. Socioeconomic status, HIV testing history, and HIV risk factors were assessed. Differences in uptake of HIV testing and counselling and in HIV infection prevalence between members of households in the lowest income quartile and the rest of the population were estimated using logistic regression. Members of households in the lowest income quartile were significantly less likely to have ever used facility-based HIV testing and counselling services than the rest of the population (odds ratio = 0.60, 95% confidence interval (CI): 0.36 to 0.97). In contrast, they were significantly more likely to use home-based HIV testing and counselling services provided during the study (adjusted odds
ratio = 1.70, 95% CI: 1.04 to 2.79). Socioeconomic differences in uptake of home-based HIV testing and counselling were not due to underlying differences in socioeconomic characteristics or HIV risk factors. The prevalence of HIV was significantly lower among members of the poorest households tested during home-based HIV testing and counselling than among the rest of the population (adjusted odds ratio = 0.37, 95% CI: 0.14 to 0.96). HIV testing and counselling uptake was high during a home-based HIV testing and counselling campaign on Likoma Island, particularly among the poorest. Home-based HIV testing and counselling has the potential to significantly reduce existing socioeconomic gradients in HIV testing and counselling uptake and help mitigate the impact of AIDS on the most vulnerable households. Editors’ note: Less than a quarter of this study population had participated in facility-based HIV testing and counselling but more than 75% accepted to be tested and immediately retrieved their test results at home. HIV prevalence overall was 8%. This is the first study to document the impact that a home-based approach can have in increasing uptake of HIV testing and counselling among young adults in the poorest households. Young women from these households were the least likely to have used facility-based testing and were the second most likely to participate in home-based HIV testing and counselling after their male counterparts. Reaching out to poorer people in their homes can help ensure that access to HIV prevention and treatment services is more equitable.

2. Pathogenesis and prognosis

Müller V, von Wyl V, Yerly S, Böni J, Klimkait T, Bürgisser P, Ledergerber B, Günthard HF, Bonhoeffer S; the Swiss HIV Cohort Study. African descent is associated with slower CD4 cell count decline in treatment-naive patients of the Swiss HIV Cohort Study. AIDS. 2009 May 20. [Epub ahead of print]

Miller and colleagues investigated the effect of descent (African versus European) on the progression of untreated HIV infections in a prospective cohort study of HIV-1-infected individuals. They estimated the linear rate of decline of the CD4 cell count and the setpoint viral load in patients with sufficient data points. The effect of descent was assessed by multivariate regression models including descent, sex, viral subtype, the earliest date of confirmed infection, age, and the baseline CD4 cell count; the rate of CD4 cell count decline was also analyzed with mixed-effect models and with matched comparisons between patients of African and European descent based on the baseline CD4 cell count. The authors found that the decline slope of the CD4 cell count was significantly less steep (+26.6 cells/mul per year; 95% confidence interval, 12.3-41.0; P < 0.001) in patients of African descent (n = 123) compared with patients of European descent (n = 463), and this effect was independent of differences in the infecting viral subtypes. Matched comparisons confirmed the effect of African descent (P < 0.001). Remarkably, the rate of CD4 cell count decline depended strongly on the viral setpoint in patients of European descent (-46.3 cells/microl per year/log10 RNA copies/ml; 95% confidence interval, -55.8 to -36.7; P < 0.001) but not in patients of African descent. Slower disease progression in patients of African descent might be related to host factors allowing better tolerance of high virus levels in patients of African descent compared with patients of European descent. Editors’ note: Faster rates of HIV disease progression have been associated with immune activation. Even HIV-negative Africans have evidence of increased immune activation, likely due to prevalent co-infections. Comparing HIV-infected individuals of African and European descent who are exposed to the same low-antigen environment of Switzerland can narrow down
differences in disease progression to viral and host factors. This study found no effect of viral sub-type suggesting that host factors must be key in the slower CD4 count decline observed in people of African origin living with HIV in Switzerland. Perhaps it is the lack of Duffy antigen receptors for chemokines (DARC-negative status) on the red blood cells in patients of African descent (see Weijing et al in HIV This Week issue 56).


Whether human immunodeficiency virus (HIV) seroconverters have been presenting with progressively lower CD4 cell counts over the course of the HIV epidemic is controversial. Additional data on whether HIV might have become more virulent on a population level (measured by post-seroconversion CD4 cell counts) may provide important insights regarding HIV pathogenesis. To determine whether post-seroconversion CD4 cell counts have changed over time, Crum-Cianflone and colleagues evaluated 2174 HIV seroconverters as part of a large cohort study during the period 1985-2007. Participants were documented antiretroviral-naive HIV seroconverters who had a CD4 cell count measured within 6 months after receiving a diagnosis of HIV infection. Multiple linear regression models were used to assess trends in initial CD4 cell counts. The mean initial CD4 cell count decreased during the study period from 632 cells/mm(3) in 1985-1990 to 553 cells/mm(3) in 1991-1995, 493 cells/mm(3) in 1996-2001, and 514 cells/mm(3) in 2002-2007. During those periods, the percentages of seroconverters with an initial CD4 cell count <350 cells/mm(3) were 12%, 21%, 26%, and 25%, respectively. In the multiple linear model, the mean decrease in CD4 cell count from 1985-1990 was 65 cells/mm(3) in 1991-1995 (P < .001), 107 cells/mm(3) in 1996-2001 (P < .001), and 102 cells/mm(3) in 2002-2007 (P < .001). Similar trends occurred with regard to CD4 cell percentage and total lymphocyte count. Similar decreases in initial CD4 cell counts were observed among African American and white persons during the epidemic. A significant decrease in initial CD4 cell counts among HIV seroconverters in the United States has occurred during the HIV epidemic. These data provide an important clinical correlate to suggestions that HIV may have adapted to the host, resulting in a more virulent infection. Editors' note: The findings for this large incident cohort (i.e., with a known date of seroconversion), in which 93% had a CD4 cell count measured within 3 months of seroconversion, suggest that initial CD4 counts among seroconverting military men (96% of the cohort were men) declined early in the HIV epidemic in the USA. Possible explanations include changes in the host, virus, or environment over time. Because the decline stabilized after introduction of potent antiretroviral therapy in 1996, it is plausible that treatment has stimulated a loss of viral fitness and diversity. The findings in the literature are conflicting and there are insufficient data to warrant a change in the assumptions about disease progression used in epidemiological modelling. Therefore further studies of the complexities of HIV virulence and host susceptibility are clearly warranted.

3. Structural determinants: prison
HIV prevalence among state prison inmates in the United States is more than five times higher than among non-incarcerated persons, but HIV transmission within U.S. prisons is sparsely documented. Jafa and colleagues investigated 88 HIV seroconversions reported from 1988-2005 among male Georgia prison inmates. They analyzed medical and administrative data to describe seroconverters' HIV testing histories and performed a case-crossover analysis of their risks before and after HIV diagnosis. The authors sequenced the gag, env, and pol genes of seroconverters' HIV strains to identify genetically-related HIV transmission clusters and antiretroviral resistance. They combined risk, genetic, and administrative data to describe prison HIV transmission networks. Forty-one (47%) seroconverters were diagnosed with HIV from July 2003-June 2005 when voluntary annual testing was offered. Seroconverters were less likely to report sex (OR [odds ratio] = 0.02, 95% CI [confidence interval]: 0-0.10) and tattooing (OR = 0.03, 95% CI: <0.01-0.20) in prison after their HIV diagnosis than before. Of 67 seroconverters' specimens tested, 33 (49%) fell into one of 10 genetically-related clusters; of these, 25 (76%) reported sex in prison before their HIV diagnosis. The HIV strains of 8 (61%) of 13 antiretroviral-naïve and 21 (40%) of 52 antiretroviral-treated seroconverters were antiretroviral-resistant. Half of all HIV seroconversions were identified when routine voluntary testing was offered, and seroconverters reduced their risks following their diagnosis. Most genetically-related seroconverters reported sex in prison, suggesting HIV transmission through sexual networks. Resistance testing before initiating antiretroviral therapy is important for newly-diagnosed inmates. Editors' note: Although HIV testing is mandatory at prison entry since 1988 in Georgia, USA and voluntary annual testing was introduced in 2003, HIV testing and counselling is not offered to inmates at the time of release from prison. HIV prevention programming to reduce risk of HIV exposure while incarcerated, an offer of pre-release HIV testing, and referral to ensure uninterrupted medical care on release are custodial corrections responsibilities. Drug resistance testing before and during antiretroviral treatment is particularly important in closed settings such as this where resistant virus clearly is being transmitted.

4. Cost-effectiveness

Nakakeeto ON, Kumaranayake L. The global strategy to eliminate HIV infection in infants and young children: a seven-country assessment of costs and feasibility. AIDS. 2009 May;23(8):987-95.

The objective of this study was to model the feasibility and affordability of the 2001 United Nations General Assembly Special Session on AIDS (UNGASS) goals to reduce mother-to-child transmission of HIV (MTCT) by 50% by 2010 and achieve 80% coverage of interventions to reduce it among women presenting for antenatal care. The cost and human resource needs of prevention of MTCT (PMTCT) and paediatric treatment were modelled for 2007-2015 and compared with the AIDS budgets and available health workforce in Burkina Faso, Cameroon, Cote d’Ivoire, Malawi, Rwanda, United Republic of Tanzania, and Zambia. Interventions used were promotion of family planning to people living with HIV, HIV testing and counselling, antiretroviral treatment to prevent MTCT and for HIV-infected children, and cotrimoxazole prophylaxis for mothers with advanced HIV infection and HIV-exposed
children. The cumulative cost from 2007 to 2015 of the intervention in the seven countries combined amounted to US$587 688 291, 86% for PMTCT and 14% for paediatric treatment. Three out of the seven countries - Rwanda, Zambia, and Burkina Faso (almost) - were predicted to have sufficient AIDS funding, but only one - Zambia - was predicted to have also sufficient human resources to scale up the interventions by 2010 and sustain them up to 2015. The cost-effectiveness would be less than US$1150 per infection prevented in fully scaled-up programmes. Scaling up PMTCT will require more funds than currently available in many countries, but human resources appear to be a greater bottleneck than funding. The authors suggest that human resource capacity be assessed when increased funds for PMTCT are requested. Editors’ note: Although these projections do not include primary prevention of HIV transmission to women of childbearing age, they do include the cost of addressing unmet family planning need among women with HIV who are of reproductive age and living in union. The model also estimated funding requirements to prevent mother-to-child transmission with antiretroviral prophylaxis, treat mothers in need of antiretroviral treatment for 9 months after the birth during breastfeeding, and treat infected children for 2 years. Although commodities (drugs, diagnostics, and supply chain management) represent 81% of the funds required and human resources represent 14%, it is the lack of sufficient numbers of health workers to implement the programme that is a major impediment in 6 of these countries striving to achieve the UNGASS goals of a 50% reduction in the incidence of HIV infection in infants by 2010.


The HIV epidemic continues to be a major issue facing Botswana, with overall adult HIV prevalence estimated to be 25.7 percent in 2007. This paper estimates the cost and impact of the draft Ministry of Health male circumcision strategy using the Decision-Makers’ Programme Planning Tool (DMPPT). Demographic data and HIV prevalence estimates from the recent National AIDS Coordinating Agency estimations are used as input to the DMPPT to estimate the impact of scaling-up male circumcision on the HIV epidemic. These data are supplemented by programmatic information from the draft Botswana National Strategy for Safe Male Circumcision, including information on unit cost and program goals. Alternative scenarios were developed in consultation with stakeholders. Results suggest that scaling-up adult and neonatal circumcision to reach 80% coverage by 2012 would result in averting almost 70,000 new HIV infections through 2025, at a total net cost of US$47 million across that same period. This results in an average cost per HIV infection averted of US$689.

Changing the target year to 2015 and the scale-up pattern to a linear pattern results in a more evenly-distributed number of male circumcisions required, and averts approximately 60,000 new HIV infections through 2025. Other scenarios explored include the effect of risk compensation and the impact of increasing coverage of general prevention interventions. Scaling-up safe male circumcision has the potential to reduce the impact of HIV in Botswana significantly; program design elements such as feasible patterns of scale-up and inclusion of counselling are important in evaluating the overall success of the program. Editors’ note: The policy development and programme planning processes for the scale-up of safe male circumcision services for heterosexual men in high HIV prevalence settings are enhanced by the use of this decision-makers’ programme planning tool developed by the Futures Institute in collaboration with UNAIDS. Both Botswana and Namibia have used the tool and several other countries have already or are currently conducting the costing studies.
that provide key inputs to determine future costs and the impact of male circumcision service scale-up on their HIV epidemics.

5. Health Information Systems


Recent changes to South Africa’s prevention of mother-to-child transmission of HIV (PMTCT) guidelines have raised hope that the national goal of reducing perinatal HIV transmission rates to less than 5% can be attained. While programmatic efforts to reach this target are underway, obtaining complete and accurate data from clinical sites to track progress presents a major challenge. Mate and colleagues assessed the completeness and accuracy of routine PMTCT data submitted to the District Health Information System in three districts of Kwazulu-Natal province, South Africa. They surveyed the completeness and accuracy of data reported for six key PMTCT data elements between January and December 2007 from all 316 clinics and hospitals in three districts. Through visits to randomly selected sites, they reconstructed reports for the same six PMTCT data elements from clinic registers and assessed accuracy of the monthly reports previously submitted to the District Health Information System. Data elements were reported only 50.3% of the time and were "accurate" (i.e. within 10% of reconstructed values) 12.8% of the time. The data element "Antenatal Clients Tested for HIV" was the most accurate data element (i.e. consistent with the reconstructed value) 19.8% of the time, while "HIV PCR testing of baby born to HIV positive mother" was the least accurate with only 5.3% of clinics meeting the definition of accuracy. Data collected and reported in the public health system across three large, high HIV-prevalence districts was neither complete nor accurate enough to track process performance or outcomes for PMTCT care. Systematic data evaluation can determine the magnitude of the data reporting failure and guide site-specific improvements in data management. Solutions are currently being developed and tested to improve data quality. Editors’ note: Beyond the finding of data missing at source, the weakest link in this data chain is the actual data collation at the clinic level, followed by lack of submission of data to the district level. Unless health workers are supported and supervised in the execution of data management tasks and unless data collection is designed in the first instance to be used locally to improve patient care, front line staff will not have the capacities nor perceive the value of data collection. Effective health information systems are simple, acceptable, timely, accurate, flexible, and useful. Only then do staff, who can improve clinical practice locally through analysis of performance and outcomes data, truly value them. This foundation stone is key to a health information system that helps national health systems assess progress towards established goals and plan future resource allocations.

6. Monitoring and Evaluation


Since 2003, the United States President’s Emergency Plan for AIDS Relief (PEPFAR) has been the most ambitious initiative to address the global HIV epidemic. However, the effect of PEPFAR on HIV-related outcomes is unknown. Bendavid and Bhattacharya set out to assess the effect of PEPFAR on HIV-related deaths, the number of people living with HIV,
and HIV prevalence in sub-Saharan Africa. Comparing trends before and after the initiation of PEPFAR’s activities they examined data from 12 African focus countries and 29 control countries with a generalized HIV epidemic from 1997 to 2007 (451 country-year observations). The intervention they were assessing was a 5-year, $15 billion program for HIV treatment, prevention, and care that started in late 2003. Outcome measures were HIV-related deaths, the number of people living with HIV, and HIV prevalence. Between 2004 and 2007, the difference in the annual change in the number of HIV-related deaths was 10.5% lower in the focus countries than the control countries (P = 0.001). The difference in trends between the groups before 2003 was not significant. The annual growth in the number of people living with HIV was 3.7% slower in the focus countries than the control countries from 1997 to 2002 (P = 0.05), but during PEPFAR’s activities, the difference was no longer significant. The difference in the change in HIV prevalence did not significantly differ throughout the study period. These estimates were stable after sensitivity analysis. The selection of the focus countries was not random, which limits the generalizability of the results. After 4 years of PEPFAR activity, HIV-related deaths decreased in sub-Saharan African focus countries compared with control countries, but trends in adult prevalence did not differ. Assessment of epidemiologic effectiveness should be part of PEPFAR’s evaluation programs. Editors’ note: The criteria for selecting PEPFAR focus countries appear to have been burden of disease, the country government’s commitment to responding to HIV, administrative capacity, and a willingness to partner with the US government. Nearly half of PEPFAR resources were spent on treatment and only one-fifth on prevention, of which one-third were earmarked for abstinence-only programmes for which the evidence base is questionable. It is not surprising then that mortality reduction rather than HIV prevalence declines appears to be the significant health-related outcome of PEPFAR from 2004 to 2007. The estimated 1.2 million deaths averted through improved treatment and care of people living with HIV in focus countries is nonetheless laudatory. In July 2008, a 48 million USD budget over 5 years was authorised for the next phase of PEPFAR and it includes a broader emphasis on strengthening health systems.

7. National responses: policy


Drawing on policy theories, an assessment was made of the perceived political feasibility of scaling-up five evidence-based interventions to curb Pakistan’s HIV epidemic: needle and syringe exchange programmes; targeted behaviour change communication; sexual health care for male and transgender sex workers; sexual and reproductive health care for female sex workers; and promoting and protecting the rights of those at greatest risk. A questionnaire was emailed to 40 stakeholders and completed by 22. They expressed their level of agreement with 15 statements for each intervention (related to variables associated with policy success). Semi-structured interviews were conducted with 12 respondents. The interventions represent considerable change from the status quo, but are perceived to respond to widely acknowledged problems. These perceptions, held by the HIV policy elite, need to be set in the context of the prevailing view that the AIDS response is not warranted given the small and concentrated nature of the epidemic and that the interventions do not resonate closely with values held by society. The interventions were perceived to be
evidence-based, supported by at least one donor and subject to little resistance from frontline staff as they will be implemented by contracted non-government organisations. The results were mixed in terms of other factors determining political feasibility, including the extent to which interventions are easy to explain, exhibit simple technical features, require few additional funds, are supported and not opposed by powerful stakeholders. The interventions stand a good chance of being implemented although they depend on donor support. The prospects for scaling them would be improved by ongoing policy analysis and strengthening of domestic constituencies among the target groups. Editors’ notes: The complex interactions among institutions, interest groups, and ideas that result in policy and policy change are the subject of policy analysis. It explains why some issues, problems, or solutions grab the attention of policy-makers. This policy analysis based on a key-informant survey suggests that while evidence contributing to the knowledge base is important, often it is superseded by the arguments and stories that resonate with decision-makers and influence their values and beliefs. Supporting the development of constituencies among highly stigmatised key populations most in need of HIV prevention and treatment services could provide a voice for the stories that can change the minds of decision-makers in Pakistan.

8. Sexual behaviour


Anal intercourse is an efficient mode of HIV transmission and may play a role in heterosexual HIV epidemics of southern Africa. However, little information is available on the anal sex practices of heterosexuals in South Africa. Kalichman and colleagues set out to examine the occurrence of anal intercourse in samples drawn from community and clinic settings. Using anonymous surveys collected from convenience samples of 2593 men and 1818 women in two townships and one large city sexually transmitted infections' clinic in Cape Town, the authors examined measures including demographics, HIV risk history, substance use, and three month retrospective sexual behaviour. A total of 14% (n = 360) men and 10% (n = 172) women reported engaging in anal intercourse in the past three months. Men used condoms during 67% and women 50% of anal intercourse occasions. Anal intercourse was associated with younger age, being unmarried, having a history of sexually transmitted infections, exchanging sex, using substances, having been tested for HIV, and testing HIV positive. Anal intercourse is reported relatively less frequently than unprotected vaginal intercourse among heterosexuals. The low prevalence of anal intercourse among heterosexuals may be offset by its greater efficiency for transmitting HIV. Anal sex should be discussed in heterosexual HIV prevention programming. Editors’ note: Most research to date has suggested that heterosexual anal intercourse in South Africa is relatively rare. After removing from the dataset the 6% of men who reported same-sex partners in the previous 3 months, this study found that 14% of men and 10% of women reported anal sex over that period. Although heterosexual anal sex was reported more frequently among STI clinic patients than township community members, no differences were found in the proportions of anal intercourse acts protected by condoms. Clearly, a focus on this sexual behaviour that carries a higher risk of HIV acquisition for women should be integrated into HIV prevention programmes aimed at fostering condom-use skills and sexual communication skills.
9. Epidemiology


Mortality in HIV-infected patients who have access to highly active antiretroviral therapy has declined in Sub-Saharan Africa, but it is unclear how mortality compares to the non-HIV-infected population. Brinkhof and colleagues compared mortality rates observed in HIV-1-infected patients starting ART with non-HIV-related background mortality in four countries in Sub-Saharan Africa. Patients enrolled in antiretroviral treatment programmes in Côte d'Ivoire, Malawi, South Africa, and Zimbabwe were included. They calculated excess mortality rates and standardised mortality ratios (SMRs) with 95% confidence intervals (CIs). Expected numbers of deaths were obtained using estimates of age-, sex-, and country-specific, HIV-unrelated, mortality rates from the Global Burden of Disease project. Among 13,249 eligible patients, 1,177 deaths were recorded during 14,695 person-years of follow-up. The median age was 34 years, 8,831 (67%) patients were female, and 10,811 of 12,720 patients (85%) with information on clinical stage had advanced disease when starting antiretroviral treatment. The excess mortality rate was 17.5 (95% CI 14.5-21.1) per 100 person-years in patients who started antiretroviral treatment with a CD4 cell count of less than 25 cells/microl and World Health Organization (WHO) stage III/IV, compared to 1.00 (0.55-1.81) per 100 person-years in patients who started with 200 cells/microl or above with WHO stage I/II. The corresponding standardised mortality ratios were 47.1 (39.1-56.6) and 3.44 (1.91-6.17). Among patients who started antiretroviral treatment with 200 cells/microl or above in WHO stage I/II and survived the first year of antiretroviral treatment, the excess mortality rate was 0.27 (0.08-0.94) per 100 person-years and the standardised mortality ratios was 1.14 (0.47-2.77). Mortality of HIV-infected patients treated with combination antiretroviral treatment in Sub-Saharan Africa continues to be higher than in the general population, but for some patients excess mortality is moderate and reaches that of the general population in the second year of antiretroviral treatment. Much of the excess mortality might be prevented by timely initiation of antiretroviral treatment. Editors' note: This study, the first to compare mortality among people starting antiretroviral treatment in Sub-Saharan Africa to non-HIV-related mortality in the general population, cannot determine the CD4 count at which antiretroviral treatment should be started in order to minimise mortality. What is clear though is that much of the excess mortality during the first two years of antiretroviral treatment - 18 times higher than the general population not infected with HIV - could be reduced by more timely initiation of treatment. Patients with very low CD4 counts and advanced clinical disease had mortality 300 times higher in the first 3 months of treatment than the general population. These results are likely applicable to many other patients receiving antiretroviral treatment in diverse settings in Africa south of the Sahara.

10. Cardiovascular morbidity and HIV

Cardiovascular disease is an increasing cause of morbidity and mortality in HIV-infected patients. However, it is controversial whether HIV infection contributes to accelerated atherosclerosis independent of traditional cardiovascular disease risk factors. In a cross-sectional study of HIV-infected participants and controls without pre-existing cardiovascular disease from the study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) and the Multi-Ethnic Study of Atherosclerosis (MESA), preclinical atherosclerosis was assessed by carotid intima-medial thickness measurements in the internal/bulb and common regions in HIV-infected participants and controls after adjusting for traditional cardiovascular disease risk factors. For internal carotid, mean intima-medial thickness was 1.17 +/- 0.50 mm for HIV-infected participants and 1.06 +/- 0.58 mm for controls (P < 0.0001). After multivariable adjustment for demographic characteristics, the mean difference of HIV-infected participants vs. controls was 0.187 mm [95% confidence interval (CI) 0.113-0.263, P < 0.0001]. Further adjustment for traditional cardiovascular disease risk factors modestly attenuated the HIV association (0.148 mm, 95% CI 0.072-0.224, P = 0.0001). For the common carotid, HIV infection was independently associated with greater intima-medial thickness (0.033 mm, 95% CI 0.010-0.056, P = 0.005). The association of HIV infection with intima-medial thickness was similar to that of smoking, which was also associated with greater intima-medial thickness (internal 0.173 mm, common 0.020 mm). Even after adjustment for traditional cardiovascular disease risk factors, HIV infection was accompanied by more extensive atherosclerosis measured by intima-medial thickness. The stronger association of HIV infection with intima-medial thickness in the internal/bulb region compared with the common carotid may explain previous discrepancies in the literature. The association of HIV infection with intima-medial thickness was similar to that of traditional cardiovascular disease risk factors, such as smoking.

Editors’ note: Although HIV infection and its therapies are associated with increases in several traditional cardiovascular disease risk factors, such as decreased high-density lipoprotein (HDL cholesterol is the good one), increased non-HDL cholesterol, and diabetes, this study of carotid wall thickness suggests that HIV infection itself confers an additional effect equivalent to a 5- to 9-year increase in age. These data suggest that women are more affected – for them the effects of HIV infection on the risk of atherosclerosis are greater than those of smoking.


Plasma soluble inflammatory molecules are associated with the risk of ischaemic cardiovascular events. Calmy and colleagues investigated whether HIV replication modified the levels of these proteins in a combination antiretroviral therapy (ART) interruption trial. In 145 HIV-infected Thai patients (62% women, median CD4 cell count 271 cells/microl, median plasma HIV-RNA 4.66 log10 copies/ml) included in the Swiss-Thai-Australia Treatment Interruption Trial (STACCATO), leptin, adiponectin, C-reactive protein, soluble vascular cell adhesion molecule-1 (s-VCAM-1), P-selectin, chemokine ligand 2, chemokine ligand 3, interleukin (IL)-6, IL-10, granulocyte macrophage colony-stimulating factor and D-dimer were measured before combination antiretroviral therapy was initiated, after combination antiretroviral therapy had suppressed HIV replication to less than 50 copies/ml plasma (median 8 months) and again 12 weeks after randomization to continued combination...
ART (n=48) or interrupted combination antiretroviral therapy (n=97). Multiple linear regression and logistic regression were used to investigate the association between each cardiovascular marker and plasma HIV-RNA. Initiation of combination antiretroviral therapy resulted in significant declines in s-VCAM-1, P-selectin, leptin and D-dimer, whereas mediators with anti-inflammatory properties, such as adiponectin and IL-10, increased. At 12 weeks after randomization, the authors found positive associations between levels of s-VCAM-1 and chemokine ligand 2 with an increase in plasma HIV-RNA (r=0.271, P=0.001 and r=0.24, P=0.005, respectively), whereas levels of adiponectin decreased for each 1 log increase in plasma HIVRNA (r=-0.24, P=0.002). Detectable IL-10 was less likely (odds ratio = 0.64, 95% confidence interval = 0.43-0.96) for each 1 log increase in plasma HIV-RNA. Plasma levels of several inflammatory, anti-inflammatory and endothelial activation markers of cardiovascular disease are associated with HIV-RNA replication.

Established cardiovascular risk factors are widely used to assess the risk of heart attacks but serum markers of endothelial activation and inflammation may also predict coronary risk. This study assessed levels of these markers before, during, and after stopping antiretroviral treatment, to tease out changes associated with HIV infection itself rather than those caused by antiretroviral drugs, some of which are known to increase heart attack risk. The association between high plasma levels of inflammatory markers and ongoing HIV-RNA replication in patients off antiretroviral treatment suggests the need to test interventions to lower these markers in people living with HIV, particularly those with detectable viral loads, to prevent cardiovascular events.

11. Trial conduct


This pilot study examined knowledge, understanding and perceived acceptability of key methodological concepts in clinical trials among injecting drug users in Sydney, Australia. Participants were clinical trial-experienced (n=17) and trial-naïve (n=99) people who inject drugs who were recruited from community needle and syringe programs, and through institutions involved in clinical trials with injecting drug using participants. Cross-sectional data were collected via a study-specific interviewer-administered survey. Following detailed verbal explanations, higher proportions of trial-experienced than trial-naïve participants demonstrated an understanding of all clinical trial concepts assessed, including single blinding (94% versus 60%); placebo (94% versus 49%); equipoise (71% versus 60%); comparison (59% versus 46%); randomisation (59% versus 21%); and double blinding (47% versus 3%). Multivariate analyses indicated a better understanding among trial-experienced participants. Participants who demonstrated an understanding of ‘placebo’ and ‘double blinding’ were significantly more likely to perceive these concepts to be acceptable than those who did not.

The results indicate the need for targeted education programs that adequately inform people who inject drugs about clinical trial concepts prior to recruitment to a clinical trial, and support adaptations of informed consent procedures to ensure trial participants’ comprehensive understanding of methodologies and their implications. Editors’ note: Despite a generally good understanding of trial concepts among people who inject drugs, with those who had already participated in a trial unsurprisingly knowing more, the perceived acceptability of equipoise, placebo, and double blinding was only 55-60%. Given that future candidate hepatitis C and HIV vaccine trials will need to recruit and
retain large numbers of injecting drug users, clinical trial literacy programmes are needed for this key population. Among the adaptations that could improve informed consent procedures would be considering them in the context of wider community engagement, with informed consent viewed as an ongoing process rather than simply a procedure at recruitment (cf UNAIDS/AVAC Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials).

12. Girls and sexual violence


Despite concern, few studies have been done about sexual violence against girls younger than 18 years of age in sub-Saharan Africa. Reza and colleagues report the prevalence and circumstances of sexual violence in girls in Swaziland, and assess the negative health consequences. They obtained data from a nationally representative sample of girls and women aged 13-24 years from selected households in Swaziland between May 15, 2007, and June 16, 2007, with a two-stage cluster design. The questionnaire examined demographics, type of sexual violence that took place before the respondent was 18 years of age, circumstances of the incident, and health-related conditions. Information was gathered from 1244 women and girls (response rate 96.3%), of whom 1242 provided retrospective responses to questions about sexual violence. The authors used regression models adjusted for relevant demographics to estimate the odds ratios for the associations between sexual violence and health-related conditions. Overall, 33.2% (95% CI 29.9-36.7) of respondents reported an incident of sexual violence before they reached 18 years of age. The most common perpetrators of the first incident were men or boys from the respondent’s neighbourhood (32.3% [28.8-36.1]) and boyfriends or husbands (26.2% [22.2-30.7]). The first incident most often took place in the respondent’s own home (26.1% [21.6-31.2]). Sexual violence was associated with reported lifetime experience of sexually transmitted diseases (adjusted OR 3.69 [95% CI 1.78-7.66]), pregnancy complications or miscarriages (3.54 [1.47-8.55]), unwanted pregnancy (2.92 [1.87-4.55]), and self-report of feeling depressed (2.30 [1.70-3.11]). Knowledge of the high prevalence of sexual violence against girls in Swaziland and its associated serious health-related conditions and behaviours should be used to develop effective prevention strategies. Editors’ note: Sexual violence occurring before age 18 years, defined as forced intercourse, coerced intercourse, attempted unwanted intercourse, unwanted touching of the respondent, or forced touching of the perpetrator, was reported by over a third of the girls and women in this nationally representative UNICEF/CDC study in Swaziland. Programmes to prevent childhood sexual abuse and minimise its devastating short-term and long-term mental, reproductive, and physical health consequences need to engage communities beyond the health sector. Increasing the safety of the school environment and travel to and from schools are first steps, but unless perpetrators are subject to social and legal sanctions, sexual abuse of girls will occur and be repeated. Since both sexual violence and intimate partner violence may have common roots and links to HIV risk, all communities, particularly those with high HIV prevalence, need to be mobilised with support from local and national leaders to confront these human rights abuses.
That was *HIV this week*, signing off.

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