Welcome to the 59th issue of *HIV This Week!* In this issue, we cover *morbidity and comorbidity* (how infecting guinea pigs reinforces the need for environmental modifications to prevent tuberculosis in humans; should treatment for *Ascaris lumbricoides*, the worm that has befriended 1.5 billion people, become routine in HIV care in helminth-endemic areas?), *gender* (actions to end economic violence to women and girls; spicy food as a dubious HIV prevention measure in Burkina Faso), *HIV in the workplace* (improving workplace HIV governance in small- and medium-sized enterprises in South Africa), *treatment as prevention* (treatment as prevention could work if condom use is maintained; population level effects of expanding treatment access in the context of comprehensive HIV prevention in British Columbia), *HIV testing* (where a child lives in Malawi and what season it is affects HIV prevalence: how HIV testing could benefit severely malnourished children), *epidemiology* (how much HIV is there in African militaries?: HIV prevalence, migration, and deportation in injecting drug users in Tijuana, Mexico), *basic science* (some HIV-exposed, non-infected infants in Kenya show evidence of immune responses in saliva; what is TRAIL and how might it help?: could acyclovir become a reverse transcriptase inhibitor in people with herpes viruses), *prevention of mother-to-child transmission* (why teen mothers in Limpopo Province, South Africa avoid services: why women in Zimbabwe can't access services: why we need to learn whether suppressive treatment of herpes simplex virus type 2 coinfection in pregnant women could decrease HIV mother-to-child transmission), *male circumcision* (overall equivalent safety of male circumcision in healthy HIV-positive and HIV-negative men in Rakai, Uganda but reason to abstain: early postoperative sex delays wound healing), *healthcare delivery* (time for joint action: what biomedical and traditional health care providers in Zambia have in common: concerted, collaborative work on reproductive health in complex emergencies brings results), and *country responses* (lessons learned about antiretroviral treatment scale-up in South Africa, Zimbabwe, and Botswana).

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1. Morbidity and comorbidity


The current understanding of airborne tuberculosis transmission is based on classic 1950s studies in which guinea pigs were exposed to air from a tuberculosis ward. Recently Escombe and colleagues recreated this model in Lima, Perú, and in this paper they report the use of molecular fingerprinting to investigate patient infectiousness in the current era of HIV infection and multidrug-resistant tuberculosis. All air from a mechanically ventilated negative-pressure HIV-tuberculosis ward was exhausted over guinea pigs housed in an airborne transmission study facility on the roof. Animals had monthly tuberculin skin tests, and positive reactors were removed for autopsy and organ culture for Mycobacterium tuberculosis. Temporal exposure patterns, drug susceptibility testing, and DNA fingerprinting of patient and animal tuberculosis strains defined infectious tuberculosis patients. Relative patient infectiousness was calculated using the Wells-Riley model of airborne infection. Over 505 study days there were 118 ward admissions of 97 HIV-positive pulmonary tuberculosis patients. Of 292 exposed guinea pigs, 144 had evidence of tuberculosis disease; a further 30 were tuberculin skin test positive only. There was marked variability in patient infectiousness; only 8.5% of 118 ward admissions by tuberculosis patients were shown by DNA fingerprinting to have caused 98% of the 125 characterised cases of secondary animal TB. 90% of tuberculosis transmission occurred from inadequately treated multi-drug resistant tuberculosis patients. Three highly infectious multi-drug resistant tuberculosis patients produced 226, 52, and 40 airborne infectious units (quanta) per hour. The study found that a small number of inadequately treated multidrug-resistant tuberculosis patients coinfected with HIV were responsible for almost all tuberculosis transmission, and some patients were highly infectious. This result highlights the importance of rapid tuberculosis drug-susceptibility testing to allow prompt initiation of effective treatment, and environmental control measures to reduce ongoing tuberculosis transmission in crowded health care settings. Tuberculosis infection control must be prioritized in order to prevent health care facilities from disseminating the drug-resistant tuberculosis that they are attempting to treat. Editors’ note: Elegantly repeating a study from the 1950s, but using molecular tools from the 21st century, this study found average patient infectiousness to be six times greater than that recorded in the 1950s. HIV must be playing some role. Ten of the 97 TB/HIV co-infected patients admitted to the ward were responsible for virtually all cases of TB among the guinea pigs and 6 of these 10 people had multidrug-resistant TB. Rapid testing of antibiotic susceptibility to identify people with MDR-TB for quick initiation of effective treatment should become routine. Natural or mechanical ventilation of TB wards, crowded waiting rooms, and emergency departments where patients with TB are likely to present will help prevent airborne transmission. Such environmental modifications are important everywhere and for everyone, but are critically important to reduce the risk of TB exposure for people living with HIV.

Several co-infections have been shown to impact the progression of HIV-1 infection. Walson and colleagues sought to determine if treatment of helminth co-infection in HIV-1-infected adults impacted markers of HIV-1 disease progression. To date, there have been no randomized trials to examine the effects of soil-transmitted helminth eradication on markers of HIV-1 progression. A randomized, double-blind, placebo-controlled trial of albendazole (400 mg daily for 3 days) in antiretroviral-naive HIV-1-infected adults (CD4 cell count >200 cells/microl) with soil-transmitted helminth infection was conducted at 10 sites in Kenya (Clinical Trials.gov NCT00130910). CD4 and plasma HIV-1 RNA levels at 12 weeks following randomization were compared in the trial arms using linear regression, adjusting for baseline values. Of 1551 HIV-1-infected individuals screened for helminth infection, 299 were helminth infected. Two hundred and thirty-four adults were enrolled and underwent randomization and 208 individuals were included in intent-to-treat analyses. Mean CD4 cell count was 557 cells/microl and mean plasma viral load was 4.75 log10 copies/ml at enrolment. Albendazole therapy resulted in significantly higher CD4 cell counts among individuals with Ascaris lumbricoides infection after 12 weeks of follow-up (+109 cells/microl; 95% confidence interval +38.9 to +179.0, P = 0.003) and a trend for 0.54 log10 lower HIV-1 RNA levels (P = 0.09). These effects were not seen with treatment of other species of soil-transmitted helminths. Treatment of Ascaris lumbricoides with albendazole in HIV-1-coinfected adults resulted in significantly increased CD4 cell counts during 3-month follow-up. Given the high prevalence of Ascaris lumbricoides infection worldwide, deworming may be an important potential strategy to delay HIV-1 progression. Editors’ note: With an estimated 1.5 billion people around the world infected by Ascaris lumbricoides, predominantly in areas with high HIV disease burden, the results of this study should make us all reflect. The CD4 count improvement and RNA drop seen in this first ever randomised controlled study of the effects of eradication of soil-associated helminths on immune system activation, in a context in which average CD4 declines are 20 to 30 cells per year, could translate into significantly delayed HIV progression and potential slowing of the need for antiretroviral treatment by at least a year. Empiric deworming of all HIV-infected persons living in helminth-infected areas deserves further study.

2. Gender


Most studies on gender-based violence (GBV) have focused on its physical, sexual, and psychological manifestations. This paper seeks to draw attention to the types of economic violence experienced by women, and describes its consequences on health and development. Economic violence experienced included limited access to funds and credit; controlling access to health care, employment, education, including agricultural resources; excluding from financial decision making; and discriminatory traditional laws on inheritance, property rights, and use of communal land. At work women experienced receiving unequal remuneration for work done equal in value to the men’s, were overworked and underpaid, and used for unpaid work outside the contractual agreement. Some experienced fraud and theft from some men,
illegal confiscation of goods for sale, and unlawful closing down of worksites. At home, some were barred from working by partners, while other men totally abandoned family maintenance to the women. Unfortunately, economic violence results in deepening poverty and compromises educational attainment and developmental opportunities for women. It leads to physical violence, promotes sexual exploitation and the risk of contracting HIV infection, maternal morbidity and mortality, and trafficking of women and girls. Economic abuse may continue even after the woman has left the abusive relationship. There is need for further large-scale studies on economic violence to women. Multi-strategy interventions that promote equity between women and men, provide economic opportunities for women, inform them of their rights, reach out to men and change societal beliefs and attitudes that permit exploitative behaviour are urgently required. Editors' note: Fighting economic violence is in everyone's best interest. Nothing less than societal transformation is required. Strategies include undertaking diplomatic and political actions, mounting boycotts, initiating lawsuits, raising public awareness, educating boys and girls that economic violence is unacceptable, attracting media attention, enacting laws that prohibit economic violence against women, and monitoring national plans of action on equality for women. Economic violence increases the risk of HIV acquisition and transmission. Economic violence is predictable and, with political commitment and societal change, it is preventable.


Despite sensitising and prevention messages, women still remain concerned about HIV in developing countries. How do they perceive the illness and methods of prevention? The objective of this study was to assess the social diagnosis of HIV infection and AIDS illness, and endogenous strategies developed by women from Gaoua. A qualitative approach was adopted, involving four focus group discussions with women from the Lobi, Birifor, Dioula and Dagara ethnic groups. An interview guide was developed for the discussions, which were carried out in local languages, tape recorded, transcribed verbatim and analysed in detail. Specific descriptions of signs/symptoms of HIV infection and HIV-related illness were given. These were: Kpéré tchi (lose weight and die) gbè yirè (twig feet) sii dan (end of life) gbè milè (thin feet), respectively for Lobi, Birifor, Dioula and Dagara. The major signs of AIDS mentioned were weight loss, appetite for meat, good meals, curly hair, large spots on the body, high fever, diarrhoea, and redness of lips. In relation to these signs, some endogenous strategies were developed by women to protect themselves against the illness, including « observation » and hot spiced meals for a few days for a partner who was absent for a long time, as well as early marriage for young girls. The social diagnosis of HIV infection and AIDS illness by a specific group like women demonstrates the gap between perceptions of the illness and prevention messages. This could help to understand that it is important to take account of communities' perceptions of illness in elaboration of prevention messages. Editors' note: In this culture, signs of immune system compromise such as wasting, Kaposi sarcoma, and oral candidiasis may be correctly perceived as indicating possible HIV infection, but curly hair and enjoying good meals, particularly those with meat, may lead women to falsely believe you are living with HIV. Unable to propose condom use, pejoratively called a 'penis sack', when their husbands return from voyages these married women rely on a home-grown HIV prevention technique of avoiding sex while feeding their husbands highly spiced food for several days to see if it provokes
diarrhoea. The first strategy likely will not work for long and the second may produce lots of false positive results. Community HIV prevention conversations have to start with beliefs and involve men if they are to lead to exploration of real options for change.

3. **HIV in the workplace**


The primary purpose of this study was to assess the role, status and scope of workplace AIDS committees as a means of effective workplace governance of AIDS impact, and their role in extending social protective HIV-related rights to employees. In-depth qualitative case studies were conducted in five South African small and medium-sized enterprises that were actively implementing HIV policies and programmes. Companies commonly implemented HIV policies and programmes through a workplace committee dedicated to HIV or a generic committee dealing with issues other than HIV. Management, through the human resources department and the occupational health practitioner often drove initial policy formulation, and had virtually sole control of the AIDS budget. Employee members of committees were mostly volunteers, and were often production or blue collar employees, while there was a notable lack of participation by white-collar employees, line management and trade unions. While the powers of workplace committees were largely consultative, employee committee members often managed in an indirect manner to secure and extend social protective rights on HIV to employees, and monitor their effective implementation in practice. In the interim, workplace committees represented one of the best means to facilitate more effective workplace HIV governance. However, the increased demands on collective bargaining as a result of an anticipated rises in HIV-related morbidity and mortality might prove to be beyond the scope of such voluntary committees in the longer term. **Editors’ note:** With human resources and occupational health representatives predominating and little trade union involvement, these committees, that have done much to extend employee rights and social protection, are ill equipped to face more serious HIV-related issues. Employee representatives and shop stewards in these companies, some of which have HIV prevalence as high as 20%, need to ensure that collective bargaining agreements include training and policy information for shop stewards. Departments of Labour should be monitoring implementation of the code of good practice on HIV in businesses of all sizes.

4. **Treatment as prevention**


A consensus statement released on behalf of the Swiss Federal Commission for HIV/AIDS suggests that people receiving effective antiretroviral therapy-ie, those with undetectable plasma HIV RNA (<40 copies per mL)-are sexually non-infectious. Wilson and colleagues analysed the implications of this statement at a population level. They used a simple mathematical model to estimate the cumulative risk of HIV transmission from effectively treated HIV-infected patients (HIV RNA <10 copies per mL) over a prolonged period. The authors investigated the risk of unprotected sexual transmission per act and cumulatively over many exposures, within couples initially discordant for HIV status. Assuming that each
couple had 100 sexual encounters per year, the cumulative probability of transmission to the serodiscordant partner each year is 0.0022 (uncertainty bounds 0.0008-0.0058) for female-to-male transmission, 0.0043 (0.0016-0.0115) for male-to-female transmission, and 0.043 (0.0159-0.1097) for male-to-male transmission. In a population of 10 000 serodiscordant partnerships, over 10 years the expected number of seroconversions would be 215 (80-564) for female-to-male transmission, 425 (159-1096) for male-to-female transmission, and 3524 (1477-6871) for male-to-male transmission, corresponding to an increase in incidence of four times compared with incidence under current rates of condom use. The analyses suggest that the risk of HIV transmission in heterosexual partnerships in the presence of effective treatment is low but non-zero and that the transmission risk in male homosexual partnerships is high over repeated exposures. If the claim of non-infectiousness in effectively treated patients was widely accepted, and condom use subsequently declined, then there is the potential for substantial increases in HIV incidence. Editors' note: This modelling suggests that, at the population level, treatment as a prevention strategy would not be an improvement over condom use. This model assumes that a threshold viral load under which transmission is very difficult does not exist, something that we do not know, and uses estimates of average HIV transmission probabilities that are unlikely to apply to all discordant couples. Nonetheless, the estimates are sobering and suggest that as a population strategy, treatment as prevention has the potential to reduce HIV epidemics only if consistent condom use is maintained. This conclusion is supported by resurgence of HIV among populations with high levels of treatment, such as men who have sex with men in Amsterdam.


Lima and colleagues developed a mathematical model using a multiple source of infection framework to assess the potential effect of the expansion of highly active antiretroviral therapy coverage among those in medical need on the number of individuals testing newly positive for human immunodeficiency virus (HIV) and on related costs in British Columbia, Canada, over the next 25 years. The model was calibrated using retrospective data describing antiretroviral therapy utilization and individuals testing newly positive for HIV in the province. Different scenarios were investigated on the basis of varying assumptions regarding drug resistance, adherence to highly active antiretroviral therapy, therapeutic guidelines, degree of highly active antiretroviral therapy coverage, and the timing of highly active antiretroviral therapy uptake. Expansion of highly active antiretroviral therapy leads to substantial reductions in the growth of the HIV epidemic and related costs. These results provide powerful additional motivation to accelerate the roll out of highly active antiretroviral therapy programmes aggressively targeting those in medical need, both for their own benefit and as a means of decreasing new HIV infections. Editors' note: This model estimates encouraging effects of treatment at the population level when all current HIV prevention modalities are maintained. These include promotion and provision of condoms, needles and syringes, and methadone maintenance, in addition to reduction in the number of sex partners. The model suggests that for expansion of treatment to be a successful complementary strategy, HIV testing must expand to increase knowledge of serostatus. Clearly, expanded access to antiretroviral treatment could be a supplement but not a replacement for current HIV prevention programming.
5. **HIV testing**


Severe malnutrition in childhood associated with HIV infection presents a serious humanitarian and public health challenge in Southern Africa. The aim of this study was to collect country wide data on HIV infection patterns in severely malnourished children to guide the development of integrated care in a resource limited setting. A cross sectional survey was conducted in 12 representative rural and urban nutrition rehabilitation units, from each of Malawi's 3 regions. All children and their caretakers admitted to each nutrition rehabilitation unit over a two week period were offered HIV counselling and testing. Testing was carried out using two different rapid antibody tests, with PCR testing for discordant results. Children under 15 months were excluded, to avoid difficulties with interpretation of false positive rapid test results. The survey was conducted once in the dry/post-harvest season, and repeated in the rainy/hungry season. 570 children were eligible for study inclusion. Acceptability and uptake of HIV testing was high: 523 (91.7%) of carers consented for their children to take part; 368 (70.6%) themselves accepted testing. Overall HIV prevalence amongst children tested was 21.6% (95% confidence intervals, 18.2-25.5%).

There was wide variation between individual nutrition rehabilitation units: 2.0-50.0%. Geographical prevalence variations were significant between the three regions (p<0.01) with the highest prevalence being in the south; Northern Region 23.1% (95%CI 14.3-34.0%), Central Region 10.9% (95%CI 7.5-15.3%) and Southern Region 36.9% (95%CI 14.3-34.0%). HIV prevalence was significantly higher in urban areas, 32.9% (95%CI 26.8-39.4%) than in rural 13.2% (95%CI 9.5-17.6%) (p<0.01). Nutrition rehabilitation unit HIV prevalence rates were lower in the rainy/hungry season 18.4% (95%CI 14.7-22.7%) than in the dry/post-harvest season 30.9% (95%CI 23.2-39.4%) (p<0.001%).

There is a high prevalence of HIV infection in severely malnourished Malawian children attending nutrition rehabilitation units with children in urban areas most likely to be infected. Testing for HIV is accepted by carers in both urban and rural areas. Nutrition rehabilitation units could act as entry points to HIV treatment and support programmes for affected children and families. Recognition of the wide geographical variation in childhood HIV prevalence will ensure that limited resources are initially targeted to areas of highest need. These findings may have implications for the other countries with similar patterns of childhood illness and food insecurity. Editors' note: The five-fold difference in HIV prevalence between the highest rate nutrition rehabilitation units in the south and the lowest rate units in the central region has practical implications for efficient resource allocation. Southern units will need larger food allocations as kids stay longer in the programme and they will require more antiretroviral drugs, cotrimoxasole and antifungal agents. Paediatric HIV testing is clearly acceptable in Malawi nutrition rehabilitation units and should be promoted everywhere that access to effective prevention, treatment, and care services can be assured.

6. **Epidemiology**

The HIV pandemic is considered a security threat. Policy-makers have warned of destabilization of militaries due to massive troop deaths. Estimates of the rate of HIV within African militaries have been as high as 90 per cent. Ba and colleagues aimed to determine if HIV prevalence within African militaries is higher than their host nation prevalence rates. Using systematic searching and access to United States Department of Defense data, the authors abstracted data on prevalence within militaries and their host communities. They conducted a random effects pooled analysis to determine differences in HIV prevalence rates in the military versus the host population, obtaining data on 21 African militaries. In general, HIV prevalence within the military was elevated compared to the general population. The differences were significant (odds ratio 1.97, 95% confidence interval: 1.58-2.45, P < 0.001). Further, inflated rates of HIV in militaries compared to non-military males of similar age were also significant (6.09, 4.47-8.30, P ≤ 0.0001). States with recent conflicts and wars had elevated military rates, but these were also not significant (P = 0.4). Population levels predicted military prevalence rates (P ≤ 0.001). HIV prevalence rates in most African militaries are significantly elevated compared to their host communities. Editors' note: The high HIV prevalence documented in the militaries of some countries in Africa is not surprising given that they are comprised predominantly of young, sexually active males. It does raise concerns about the potential for shortages in the numbers of qualified and experienced military personnel available for deployment, particularly when the armed forces play a key role in maintaining and promoting peace in the region. Intensified HIV prevention and antiretroviral treatment are key to maintaining a healthy military.


HIV prevalence is rising, especially among high risk females in Tijuana, Baja California, a Mexico-US border city situated on major migration and drug trafficking routes. Strathdee and colleagues compared factors associated with HIV infection among male and female injection drug users in Tijuana in an effort to inform HIV prevention and treatment programmes. Injection drug users aged ≥ 18 years were recruited using respondent-driven sampling and underwent testing for HIV, syphilis and structured interviews. Logistic regression identified correlates of HIV infection, stratified by gender. Among 1056 injection drug users, most were Mexican-born but 67% were born outside Tijuana. Reasons for moving to Tijuana included deportation from the US (56% for males, 29% for females), and looking for work/better life (34% for females, 15% for males). HIV prevalence was higher in females versus males (10.2% vs. 3.5%, p = 0.001). Among females (N=158), factors independently associated with higher HIV prevalence included younger age, lifetime syphilis infection and living in Tijuana for longer durations. Among males (N=898), factors independently associated with higher HIV prevalence were syphilis titres consistent with active infection, being arrested for having 'track-marks', having larger numbers of recent injection partners and living in Tijuana for shorter durations. An interaction between gender and number of years lived in Tijuana regressed on HIV infection was significant (p = 0.03). Upon further analysis, deportation from the U.S. explained the association between shorter duration lived in Tijuana and HIV infection among males; odds of HIV infection were four-fold higher among male injectors deported from the US, compared to other males, adjusting
for all other significant correlates (p = 0.002). Geographic mobility has a profound influence on Tijuana’s evolving HIV epidemic, and its impact is significantly modified by gender. Future studies are needed to elucidate the context of mobility and HIV acquisition in this region, and whether US immigration policies adversely affect HIV risk. Editors’ note: These findings suggest that geographic mobility may have had a differential effect on the risk of HIV infection among male and female injecting drug users in Tijuana, with a three-fold higher HIV prevalence documented among the women. However, its cross-sectional design means that a causal relationship cannot be confirmed. Nonetheless, supportive programmes for migrants, deportees, and other displaced persons on both sides of the U.S.-Mexico border could help mitigate the effects of social disruption and displacement.

7. Basic science


Humoral immunity, and specifically immunoglobulin A (IgA) that is directed against human immunodeficiency virus (HIV)-1, may contribute to protection against HIV-1 acquisition at mucosal surfaces. HIV-1-specific IgA has been detected in genital tract secretions of HIV-1-uninfected commercial sex workers with HIV-1 exposure, and may be produced in parotid saliva by infants exposed orally to HIV-1 during delivery and breastfeeding. To explore this hypothesis, Farquhar and colleagues collected saliva from 145 infants aged ≤ 6 months enrolled in a perinatal HIV-1 transmission study in Nairobi and from 55 control infants without HIV-1 exposure who were born to HIV-1-seronegative mothers. Among the 145 infants, 115 (79%) remained uninfected during the 12-month study period and 30 (21%) became HIV-1-infected during follow-up. Nine (8%) of the 115 HIV-1-exposed, uninfected infants had detectable levels of HIV-1 gp160-specific IgA compared with four (13%) of 30 infected infants and none of 55 control infants (P = 0.47 and P = 0.03 respectively). Among the nine HIV-1-exposed, uninfected infants with positive assays, median age was 1 month and none acquired HIV-1 during follow-up. The authors conclude that HIV-1-specific salivary IgA responses may be generated by very young infants exposed perinatally to maternal HIV-1. Mucosal responses would be an appropriate target for paediatric vaccines against breast milk HIV-1 transmission. Editors’ note: Waning HIV-specific immunoglobulin G (IgG) in an infant’s saliva represents passive transfer of maternal antibodies, whereas detection of HIV-specific IgA indicates infant response to HIV exposure. Although no association was seen with a reduced risk of acquiring HIV, the results of this study provide some evidence that natural HIV exposure via the oral route during delivery and breastfeeding can stimulate a humoral immune response (salivary HIV specific IgA) in infants younger than 6 months of age.


During uncontrolled HIV disease, both tumour-necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL) and TRAIL receptor expression are increased. Enhanced TRAIL sensitivity is due to TRAIL receptor up-regulation induced by gp120. As a result of successful antiretroviral therapy TRAIL is down-regulated, and there are fewer TRAIL-
sensitive cells. In this setting, Shepard and colleagues hypothesized that all cells that contain virus, including those productively- and latently-infected, have necessarily been "primed" by gp120 and remain TRAIL-sensitive, whereas uninfected cells remain relatively TRAIL-resistant. The authors evaluated the immunologic and antiviral effects of TRAIL in peripheral blood lymphocytes collected from HIV-infected patients with suppressed viral replication. The peripheral blood lymphocytes were treated with recombinant TRAIL or an equivalent amount of bovine serum albumin as a negative control. Treated cells were then analyzed by quantitative flow cytometry, ELISPOT for CD4+ and CD8+ T-cell function, and limiting dilution microculture for viral burden. Alterations in the cytokine milieu of treated cells were assessed with a multiplex cytokine assay. Treatment with recombinant TRAIL in vitro reduced viral burden in lymphocytes collected from HIV-infected patients with suppressed viral load. TRAIL treatment did not alter the cytokine milieu of treated cells. Moreover, treatment with recombinant TRAIL had no adverse effect on either the quantity or function of immune cells from HIV-infected patients with suppressed viral replication. In conclusion, TRAIL treatment may be an important adjunct to antiretroviral therapy, even in patients with suppressed viral replication, perhaps by inducing apoptosis in cells with latent HIV reservoirs. The absence of adverse effect on the quantity or function of immune cells from HIV-infected patients suggests that there is not a significant level of "bystander death" in uninfected cells. Editors' note: The mechanism by which activation of TRAIL signalling induces reductions in viral load is unclear and this work is 'in vitro' (meaning in the laboratory, as opposed to 'in vivo' meaning in humans). TRAIL signalling might induce the death of infected cells without killing other cells or reduce viral load in some other way without causing adverse effects. There are very preliminary but nonetheless intriguing results.


For most viruses, there is a need for antimicrobials that target unique viral molecular properties. Acyclovir is one such drug. It is activated into a human herpesvirus DNA polymerase inhibitor exclusively by human herpesvirus kinases and, thus, does not suppress other viruses. Here, Lisco and colleagues show that acyclovir suppresses HIV-1 in herpesvirus-coinfected human tissues, but not in HHV-free tissue or cell cultures. However, addition of HHV-6-infected cells renders these cultures sensitive to anti-HIV acyclovir activity. The authors hypothesized that such HIV suppression requires acyclovir phosphorylation by human herpesvirus kinases. Indeed, an acyclovir monophosphorylated prodrug bypasses the human herpesvirus requirement for HIV suppression. Furthermore, phosphorylated acyclovir directly inhibits HIV-1 reverse transcriptase, terminating DNA chain elongation, and can trap reverse transcriptase at the termination site. These data suggest that acyclovir anti-HIV-1 activity may contribute to the response of HIV/human herpesvirus-coinfected patients to acyclovir treatment and could guide strategies for the development of new HIV-1 reverse transcriptase inhibitors. Editors' note: This study suggests that acyclovir, commonly used to treat herpes simplex, could potentially have a direct effect on HIV beyond the indirect effects that suppression of another infection can have on HIV. This direct effect appears to rely on the presence of a human herpes virus, such as the ubiquitous human herpes virus-6, to provide enzymes that
phosphorylate acyclovir in infected cells. After further conversion into its antiviral active form, acyclovir then fights herpes but it might also fight HIV, because this active form happens to be a reverse transcriptase inhibitor. Clinical trials are needed to determine whether there is a potential role in combination HIV treatment of low toxicity, low cost acyclovir, a drug that has been used for over 30 years.

8. Prevention of mother-to-child HIV transmission


In this article, Varga and colleagues examine barriers to HIV testing uptake and participation in prevention of mother-to-child HIV transmission services among adolescent mothers aged 15 to 19 years in rural and urban Limpopo Province, South Africa. The authors used the narrative research method involving key informants constructing typical case studies of adolescent experiences with HIV testing and entry into prevention of mother-to-child HIV transmission. Case studies formed the basis of a community-based questionnaire and focus group discussions with adolescent mothers. Client-counsellor dynamics during pre-test counselling were pivotal in determining uptake and participation, and counsellor profile strongly influenced the nature of the interaction. Other factors found to influence adherence to prevention of mother-to-child HIV transmission recommendations included HIV and early premarital pregnancy stigma, fear of a positive test result, and concerns over confidentiality and poor treatment by health care providers. Adolescents described elaborate strategies to avoid HIV disclosure to labour and delivery staff, despite knowing this would mean no antiretroviral therapy for their newborn infants. Theoretical, methodological, and programmatic implications of study findings are also discussed. Editors' note: By age 19, 30% of South African adolescent girls have been pregnant. Surveillance data estimate that more than 15% of pregnant adolescents are HIV-positive. The double stigma of pregnancy and HIV infection along with negative attitudes among health care workers poorly prepared to deal with adolescents underpin poor programme uptake. Sufficient training and adequate time to ensure supportive interactions during the initial pre-test counselling contact is an obvious first step to healthier outcomes for both adolescent mothers and their infants.


In developing countries, mother-to-child transmission of HIV is responsible for 5-10% of all new HIV infections. HIV positive mothers can transmit HIV to their babies during pregnancy, childbirth and breast-feeding. Anti-retroviral drugs are effective in reducing the risk of mother-to-child transmission of HIV. The main focus of this study was to describe mothers' attitudes towards using services for preventing mother-to-child transmission of HIV. A non-experimental, descriptive design with a survey approach was used. The study was conducted at one hospital in Bulawayo, Zimbabwe that offers both prenatal clinic and maternity, including prevention of mother-to-child transmission, services. Fifty pregnant women, who attended prenatal clinics in Bulawayo and who booked to deliver their babies in the hospital's maternity section, were interviewed. A structured interview survey was used to collect data. The interviewed women required more knowledge about preventing mother-to-
child transmission of HIV. Many pregnant women would not use the services available for the prevention of mother-to-child transmission of HIV, for personal, financial and cultural reasons. However, the most important barriers preventing pregnant women from using free prevention of mother-to-child transmission services were structural ones. Only pregnant women who attended prenatal clinics and delivered their babies in hospital could access these services. Prenatal and delivery services might be beyond the financial reach of many Zimbabwean women, making prevention of mother-to-child transmission services inaccessible to them. Free infant formula could not be accessed at hospitals and clinics because of transport costs. Editors’ note: This small study in one site highlights practical constraints that must be overcome to achieve universal access to prevention of mother-to-child transmission. Although HIV testing and counselling, antiretroviral prophylaxis, and counselling and support for safe infant feeding were available free of charge, basic pre-natal, delivery, and post-natal services were not. When women cannot access these because of transport or financial constraints, prevention of mother-to-child transmission doesn’t even make it to the table.


Bollen and colleagues aimed to evaluate the association between maternal herpes simplex virus type 2 seropositivity and genital herpes simplex virus type 2 shedding with perinatal HIV transmission. Women who participated in a 1996-1997 perinatal HIV transmission prevention trial in Thailand were evaluated. In this non-breastfeeding population, women were randomized to zidovudine or placebo from 36 weeks gestation through delivery; maternal plasma and cervicovaginal HIV viral load and infant HIV status were determined for the original study. Stored maternal plasma and cervicovaginal samples were tested for herpes simplex virus type 2 antibodies by enzyme-linked immunoassay and for herpes simplex virus type 2 DNA by real-time PCR, respectively. Among 307 HIV-positive women with available samples, 228 (74.3%) were herpes simplex virus type 2 seropositive and 24 (7.8%) were shedding herpes simplex virus type 2. Herpes simplex virus type 2 seropositivity was associated with overall perinatal HIV transmission [adjusted odds ratio, 2.6; 95% confidence interval, 1.0-6.7], and herpes simplex virus type 2 shedding was associated with intrapartum transmission (adjusted odds ratio, 2.9; 95% confidence interval, 1.0-8.5) independent of plasma and cervicovaginal HIV viral load, and infant HIV status were determined for the original study. Among 307 HIV-positive women with available samples, 228 (74.3%) were herpes simplex virus type 2 seropositive and 24 (7.8%) were shedding herpes simplex virus type 2. Herpes simplex virus type 2 seropositivity was associated with overall perinatal HIV transmission [adjusted odds ratio, 2.6; 95% confidence interval, 1.0-6.7], and herpes simplex virus type 2 shedding was associated with intrapartum transmission (adjusted odds ratio, 2.9; 95% confidence interval, 1.0-8.5) independent of plasma and cervicovaginal HIV viral load, and zidovudine treatment. Median plasma HIV viral load was higher among herpes simplex virus type 2 shedders (4.2 vs. 4.1 log(10) copies/ml; P = 0.05), and more shedders had quantifiable levels of HIV in cervicovaginal samples, compared with women not shedding herpes simplex virus type 2 (62.5 vs. 34.3%; P = 0.005). The authors found an increased risk of perinatal HIV transmission among herpes simplex virus type 2 seropositive women and an increased risk of intrapartum HIV transmission among women shedding herpes simplex virus type 2. These novel findings suggest that interventions to control herpes simplex virus type 2 infection could further reduce perinatal HIV transmission. Editors’ note: Co-infected women had higher HIV plasma viral loads than did women without herpes simplex virus-2 (HSV-2) in this study which may explain why women with HSV-2 were more likely to transmit to their infants. If these findings are replicated among women receiving currently recommended drugs for prophylaxis of mother-to-child transmission, further evaluation is warranted of adding suppressive
treatment for HSV-2 to help prevent mother-to-child transmission. Acyclovir, a drug that is well tolerated in pregnancy, is off patent and cheap.

9. **Male circumcision**


The objective of the study was to compare rates of adverse events related to male circumcision in HIV-positive and HIV-negative men in order to provide guidance for male circumcision programmes that may provide services to HIV-infected and uninfected men. A total of 2,326 HIV-negative and 420 HIV-positive men (World Health Organization stage I or II and CD4 counts > 350 cells/mm(3)) were circumcised in two separate but procedurally identical trials of male circumcision for HIV and/or sexually transmitted infection prevention in rural Rakai, Uganda. Participants were followed at 1-2 days and 5-9 days, and at 4-6 weeks, to assess surgery-related adverse events, wound healing, and resumption of intercourse. Adverse event risks and wound healing were compared in HIV-positive and HIV-negative men. Adjusted odds ratios were estimated by multiple logistic regression, adjusting for baseline characteristics and postoperative resumption of sex. At enrolment, HIV-positive men were older, more likely to be married, reported more sexual partners, less condom use, and higher rates of sexually transmitted disease symptoms than HIV-negative men. Risks of moderate or severe adverse events were 3.1/100 and 3.5/100 in HIV-positive and HIV-negative participants, respectively (Adjusted odds ratio 0.91, 95% confidence interval [CI] 0.47-1.74). Infections were the most common adverse events (2.6/100 in HIV-positive versus 3.0/100 in HIV-negative men). Risks of other complications were similar in the two groups. The proportion with completed healing by 6 weeks post surgery was 92.7% in HIV-positive men and 95.8% in HIV-negative men (p = 0.007). Adverse events were more common in men who resumed intercourse before wound healing compared to those who waited (Adjusted odds ratio 1.56, 95% CI 1.05-2.33). In conclusion, the overall safety of male circumcision was comparable in asymptomatic HIV-positive and HIV-negative men, although healing was somewhat slower among the HIV infected. All men should be strongly counselled to refrain from intercourse until full wound healing is achieved. Trial registration: [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov); for HIV-negative men, and for HIV-positive men. Editors' note: The finding that there is no difference in the risk of adverse events for asymptomatic HIV-positive and HIV-negative men is encouraging because HIV testing is not mandatory for circumcision. HIV testing is a key voluntary component of a comprehensive service but all men who are in good health may undergo circumcision whether they decide to be tested or not. They should all be advised that early resumption of sexual intercourse has been shown to delay wound healing. As well, preliminary data from other studies and common sense concur that sex before complete wound healing may increase their risk of acquiring HIV, rather than protecting them, and may increase their risk of transmitting HIV to a sexual partner if they already have HIV infection.

With the growing incidence of HIV, there is a desperate need to develop simple, cheap, and effective new ways of preventing HIV infection. Male circumcision reduces the risk of infection by about 60%, probably because of the removal of the Langerhans cells which are abundant in the inner foreskin and are the primary route by which HIV enters the penis. Langerhans cells form a vital part of the body's natural defence against HIV and only cause infection when they are exposed to high levels of HIV virions. Rather than removing this natural defence mechanism by circumcision, it may be better to enhance it by thickening the layer of keratin overlying the Langerhans cells, thereby reducing the viral load to which they are exposed. Pask and colleagues investigated the ability of topically administered oestrogen to induce keratinization of the epithelium of the inner foreskin. Histochemically, the whole of the foreskin is richly supplied with oestrogen receptors. The epithelium of the inner foreskin, like the vagina, responds within 24 hours to the topical administration of oestriol by keratinization, and the response persists for at least 5 days after the cessation of the treatment. Oestriol, a cheap, readily available natural oestrogen metabolite, rapidly keratinizes the inner foreskin, the site of HIV entry into the penis. This thickening of the overlying protective layer of keratin should reduce the exposure of the underlying Langerhans cells to HIV virions. This simple treatment could become an adjunct or alternative to surgical circumcision for reducing the incidence of HIV infection in men.

Editors' note: Langerhans cells are no more abundant in the inner foreskin than they are in the outer foreskin or shaft of the penis, but the thinner protective keratin layer of the inner foreskin makes them more accessible for HIV. The abstract does not describe the methodology. Two sexually inactive uncircumcised men applied oestrogen cream to the inner foreskin daily for 14 days before undergoing circumcision. Contact smears taken daily and surgical tissue sections were examined. Keratinisation increased for these two men but this does not translate into protection against HIV. Clinical trials to evaluate efficacy would be required before conclusions could be drawn about whether oestrogen cream plays any role in HIV prevention for insertive men.

10. Healthcare delivery


Kaboru and colleagues aimed to explore biomedical and traditional health care providers' perceptions of good quality of care and opinions on weaknesses in the services they provide to patients with HIV and other sexually transmitted infections. Using data from a cross-sectional survey, the authors post-coded two open-ended questions related to biomedical and traditional health care providers' perceptions on good quality of care and on provided care. The post-coding was done following Donabedian's framework of assessment of quality of care and allowed transformation of qualitative data into quantitative. The analysis is based on comparison of frequencies, proportions, and subsequent chi-square tests and odds ratios. The study set in Ndola and Kabwe, Zambia measured proportions of responses from 152 biomedical and 144 traditional health care providers. Substantial proportions of providers from both sectors perceived drugs availability (63% of biomedical and 70% of traditional health care providers) and welcoming attitude (73% of biomedical and 64% of traditional health care providers) as important components of good quality care. Biomedical health care providers were more likely than traditional health care providers to mention proper
examination, medical management (provider’s technical ability) and explanation of causes and prognosis of the disease as important. More traditional health care providers than biomedical ones cited short waiting time and cost of care. A majority of biomedical health care providers (87%) and of traditional health care providers (80%) reported deficiencies in their sexually transmitted infection- and HIV-related services. Both groups regarded training of providers and nutritional support and health education to patients as lacking. None of the traditional health care providers alluded to voluntary counselling and testing or supportive/home-based care as aspects needing improvement. Drugs availability and welcoming attitude were two aspects of quality highly valued by biomedical and traditional health care providers. Future collaborative interventions need to respond to aspects of joint concern including training of providers, nutritional support, and health education to patients. Further, there is an imperative of expanding and adapting voluntary counselling and testing, home-based care and palliative care to traditional health care providers for better care of HIV and other sexually transmitted infections. Editors’ note: This study comparing the views of both traditional and biomedical care providers provides food for thought on how to improve quality of care for patients who access either or both types of providers. Better collaboration for joint health action in the community could reduce drug interactions, decrease costs for patients, and enhance the comparative contribution of each type of provider.


Continued political and civil unrest in low-resource countries underscores the ongoing need for specialised reproductive health services for displaced people. Displaced women particularly face high maternal mortality, unmet need for family planning, complications following unsafe abortion, and gender-based violence, as well as sexually transmitted diseases, including HIV. Relief and development agencies and UN bodies have developed technical materials, made positive policy changes specific to crisis settings and are working to provide better reproductive health care. Substantial gaps remain, however. The collaboration within the field of reproductive health in crises is notable, with many agencies working in one or more networks. The five-year RAISE Initiative brings together major United Nations agencies and non-governmental organisations from the fields of relief and development, and builds on their experience to support reproductive health service delivery, advocacy, clinical training and research. The readiness to use common guidance documents, develop priorities jointly and share resources has led to smoother operations and less overlap than if each agency worked independently. Trends in the field, including greater focus on internally displaced persons and those living in non-camp settings, as well as refugees in camps, the protracted nature of emergencies, and an increasing need for empirical evidence, will influence future progress. Editors’ note: The RAISE (Reproductive Health Access, Information, and Services in Emergencies) Initiative is a partnership with a long-term perspective (2006-2011) of Columbia University and Marie Stopes International with United Nations, humanitarian, and development organisations. RAISE and other networks arose from the collaborative work of 40 UN, government, and non-governmental organisations that formed the Inter-Agency Working Group on Reproductive Health in Crises (IAWG) in 1995. Since collaborative work across this field has been long lasting and productive, it is useful to examine what underpinned both the trends and key advances.
11. Country responses


Over the past 3 years, significant strides have been made in the effort to provide antiretroviral therapy to the millions of people worldwide who require treatment for HIV. In 2006, 1.3 million people had initiated antiretroviral therapy in sub-Saharan Africa, which is a 10-fold increase over the number who had access to treatment 3 years prior. Although this progress should be acknowledged, achieving universal access will require much more work. As countries initiate large-scale treatment programmes, many political, social, economic, and operational challenges have become evident. South Africa, Zimbabwe, and Botswana are three neighbouring countries engaged in antiretroviral therapy roll-out. This article describes the HIV epidemic in these three countries, details the most critical challenges inhibiting the progression of antiretroviral therapy roll-out, and highlights successes within each setting. Editors' note: This interesting comparative analysis of these three neighbours reveals that although political will and economic stability are predictors of success, weak health care infrastructure and lack of integration of HIV care with primary health care pose challenges to sustained antiretroviral treatment programmes.

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