

## *HIV This Week*: what scientific journals said

Welcome to issue fifty-four of *HIV This Week*! In this issue, we cover **breast-feeding** (extended antiretroviral prophylaxis in a Malawi trial helps a bit but more is needed; abrupt early weaning fails to improve HIV-free survival and is harmful for infected kids in Zambia), **structural determinants and vulnerability** (insights from the analysis of the political economy of sex in South Africa; adolescent girls who have lost their mothers in Zimbabwe), **serodiscordant couples** (why urban heterosexuals in Zambia and Rwanda need to know their HIV status), **sexual transmission and prevention** (viral suppression in the Netherlands: initial success is not the whole story; antiretroviral treatment and the genital tract: secrets revealed; Spanish men pay to score..... sometimes an own goal?), **prevention of mother-to-child transmission** (catching up on the labour ward in rural India), **sexual and reproductive health** (short-term findings on injectable hormones and antiretroviral therapy: what about the long term?), **health care delivery** (finding solutions in Kibera, Kenya), **genetics** (genes and drugs - pharmacogenetics; cell death and genes - immunogenetics), **treatment and care** (rising cancer rates in people living with HIV in the United States: what can be done?), and **basic science** (re-energising exhausted polyfunctional CD8+ T cells).

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### **1. Breastfeeding**

Kumwenda NI, Hoover DR, Mofenson LM, Thigpen MC, Kafulafula G, Li Q, Mipando L, Nkanaunena K, Mebrahtu T, Bulterys M, Fowler MG, Taha TE. Extended Antiretroviral Prophylaxis to Reduce Breast-Milk HIV-1 Transmission. *N Engl J Med*. 2008 Jun 4. Epub ahead of print.

Effective strategies are urgently needed to reduce mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) through breast-feeding in resource-limited settings. Women with HIV-1 infection who were breast-feeding infants were enrolled in a randomized, phase 3 trial in Blantyre, Malawi. At birth, the infants were randomly assigned to one of

three regimens: single-dose nevirapine plus 1 week of zidovudine (control regimen) or the control regimen plus daily extended prophylaxis either with nevirapine (extended nevirapine) or with nevirapine plus zidovudine (extended dual prophylaxis) until the age of 14 weeks. Using Kaplan-Meier analyses, Kumwenda and colleagues assessed the risk of HIV-1 infection among infants who were HIV-1-negative on DNA polymerase-chain-reaction assay at birth. Among 3016 infants in the study, the control group had consistently higher rates of HIV-1 infection from the age of 6 weeks through 18 months. At 9 months, the estimated rate of HIV-1 infection (the primary end point) was 10.6% in the control group, as compared with 5.2% in the extended-nevirapine group ( $P<0.001$ ) and 6.4% in the extended-dual-prophylaxis group ( $P=0.002$ ). There were no significant differences between the two extended-prophylaxis groups. The frequency of breast-feeding did not differ significantly among the study groups. Infants receiving extended dual prophylaxis had a significant increase in the number of adverse events (primarily neutropenia) that were deemed to be possibly related to a study drug. In conclusion, extended prophylaxis with nevirapine or with nevirapine and zidovudine for the first 14 weeks of life significantly reduced postnatal HIV-1 infection in 9-month-old infants. **Editors' note: The protective efficacy of both extended prophylaxis regimens was more than 60% at 14 weeks, significantly better than a control regimen of single dose nevirapine and 1 week of zidovudine. However, there were significantly more infants with serious adverse events in the dual extended prophylaxis group than in either of the other groups and HIV infection rates were similar for all three groups from age 14 weeks to 9 months, once drug was withdrawn. Based on these findings, a practical approach would be to consider prolonging the extended nevirapine regimen for the duration of breast-feeding. Clearly, serious study is now needed of the risks and benefits for mothers and babies of uninterrupted maternal antiretroviral therapy in pregnancy and beyond, irrespective of CD4 count, for HIV-positive women in settings in which breastfeeding is the safest option for infants.**

Kuhn L, Aldrovandi GM, Sinkala M, Kankasa C, Semrau K, Mwiya M, Kasonde P, Scott N, Vwalika C, Walter J, Bulterys M, Tsai WY, Thea DM; the Zambia Exclusive Breastfeeding Study. Effects of Early, Abrupt Weaning for HIV-free Survival of Children in Zambia. *N Engl J Med*. 2008 Jun 4. Epub ahead of print.

In low-resource settings, many programs recommend that women who are infected with the human immunodeficiency virus (HIV) stop breast-feeding early. Kuhn and colleagues conducted a randomized trial to evaluate whether abrupt weaning at 4 months as compared with the standard practice has a net benefit for HIV-free survival of children. The authors enrolled 958 HIV-infected women and their infants in Lusaka, Zambia. All the women planned to breast-feed exclusively to 4 months; 481 were randomly assigned to a counselling program that encouraged abrupt weaning at 4 months, and 477 to a program that encouraged continued breast-feeding for as long as the women chose. The primary outcome was either HIV infection or death of the child by 24 months. In the intervention group, 69.0% of the mothers stopped breast-feeding at 5 months or earlier; 68.8% of these women reported the completion of weaning in less than 2 days. In the control group, the median duration of breast-feeding was 16 months. In the overall cohort, there was no significant difference between the groups in the rate of HIV-free survival among the children; 68.4% and 64.0% survived to 24 months without HIV infection in the intervention and control groups, respectively ( $P=0.13$ ). Among infants who were still being breast-fed and were not infected with HIV at 4 months, there was no significant difference between the groups in HIV-free

survival at 24 months (83.9% and 80.7% in the intervention and control groups, respectively;  $P=0.27$ ). Children who were infected with HIV by 4 months had a higher mortality by 24 months if they had been assigned to the intervention group than if they had been assigned to the control group (73.6% vs. 54.8%,  $P=0.007$ ). In conclusion, early, abrupt cessation of breast-feeding by HIV-infected women in a low-resource setting, such as Lusaka, Zambia, does not improve the rate of HIV-free survival among children born to HIV-infected mothers and is harmful to HIV-infected infants. **Editors' note: The fact that only two-thirds of the women assigned to early abrupt weaning at 4 months did so, despite provision of free formula, complementary food, and home counselling visits, affected the intention-to-treat analysis. Even had the trial found an HIV-free survival advantage at 24 months for early abrupt weaning, this practice might not have been acceptable in this population where breastfeeding into the second year of life is the norm. WHO currently advises exclusive breastfeeding to 6 months of age and continued breastfeeding with complementary foods after 6 months if replacement feeding is still not acceptable, feasible, affordable, sustainable, and safe (AFASS). Most importantly, this trial demonstrated clear harm for infants who were already HIV-infected at 4 months and who were abruptly weaned. Now, it is no longer ethical to design trials in which HIV-exposed infants are randomly assigned to infant feeding interventions without knowledge of their HIV status.**

## ***2. Structural determinants and vulnerability***

Hunter M. The changing political economy of sex in South Africa: the significance of unemployment and inequalities to the scale of the AIDS pandemic. *Soc Sci Med.* 2007;64(3):689-700.

Between 1990 and 2005, HIV prevalence rates in South Africa jumped from less than 1% to around 29%. Important scholarship has demonstrated how racialized structures entrenched by colonialism and apartheid set the scene for the rapid unfolding of the AIDS pandemic, like other causes of ill-health before it. Of particular relevance is the legacy of circular male-migration, an institution that for much of the 20th century helped to propel the transmission of sexually transmitted infections among black South Africans denied permanent urban residence. But while the deep-rooted antecedents of AIDS have been noted, less attention has been given to more recent changes in the political economy of sex, including those resulting from the post-apartheid government's adoption of broadly neo-liberal policies. As an unintentional consequence, male migration and apartheid can be seen as almost inevitably resulting in AIDS, a view that can disconnect the pandemic from contemporary social and economic debates. Combining ethnographic, historical, and demographic approaches, and focusing on sexuality in the late apartheid and early post-apartheid periods, this article outlines three interlinked dynamics critical to understanding the scale of the AIDS pandemic: (1) rising unemployment and social inequalities that leave some groups, especially poor women, extremely vulnerable; (2) greatly reduced marital rates and the subsequent increase of one person households; and (3) rising levels of women's migration, especially through circular movements between rural areas and informal settlements/urban areas. As a window into these changes, the article gives primary attention to the country's burgeoning informal settlements--spaces in which HIV rates are reported to be twice the national average--and to connections between poverty and money/sex exchanges. **Editors' note: Political economy analyses help conceptualise HIV as a symptom of 'structural violence' with sex as a mode of transmission. Housing, employment, and**

social equality are clearly linked to HIV, both historically and contemporarily, and help explain the striking scale of the South African epidemic. This article, which suggests ways to reconfigure the response to AIDS around a more politically enabling agenda, makes for thought-provoking reading.

Kang M, Dunbar M, Laver S, Padian N. University of California Programme in Women's Health, University of California-San Francisco, 50 Beale Street, San Francisco, CA 94105, USA. Maternal versus paternal orphans and HIV/STI risk among adolescent girls in Zimbabwe. *AIDS Care*. 2008;20(2):214-7.

The AIDS epidemic has contributed to a drastic increase in the number of orphans in Zimbabwe. Orphans (whether orphaned by AIDS or other causes) have been shown to have economic and educational disadvantages as well as poor reproductive health outcomes. Kang and colleagues recruited a convenience sample of 200 girls in a peri-urban area of Zimbabwe to examine the impact of orphan status (compared to non-orphans) on household composition, education, risk behaviour, pregnancy and prevalent HIV and HSV-2 infection. In the study population, maternal orphans were more likely to be in households headed by themselves or a sibling, to be sexually active, to have had a sexually transmitted infection, to have been pregnant and to be infected with HIV. Paternal orphans were more likely to have ever been homeless and to be out of school. The findings suggest that maternal care and support is important for HIV prevention. This finding corroborates previous research in Zimbabwe and has implications for intervention strategies among orphan girls. **Editors' note: Because of recruitment methodology, these results are not generalizable, however they do provide food for thought. Although paternal orphanhood had more of an impact on household financial stability and orphaned girls' educational attainment, the loss of a mother affected behavioural risk and biological outcomes (HIV, HSV-2). Keeping mothers alive helps reduce sexual risk in adolescent girls. How would orphaned adolescent girls in Zimbabwe benefit from support and mentoring by women in their communities?**

### 3. *Serodiscordant couples*

Kristin L Dunkle, Rob Stephenson, Etienne Karita, Elwyn Chomba, Kayitesi Kayitenkore, Cheswa Vwalika, Lauren Greenberg, Susan Allen. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. *Lancet*. 2008;371(9631):2183-91.

Sub-Saharan Africa has a high rate of HIV infection, most of which is attributable to heterosexual transmission. Few attempts have been made to assess the extent of HIV transmission within marriages, and HIV prevention efforts remain focused on abstinence and non-marital sex. Dunkle and colleagues aimed to estimate the proportion of heterosexual transmission of HIV which occurs within married or cohabiting couples in urban Zambia and Rwanda each year. The authors used population-based data from Demographic and Health Surveys (DHS) on heterosexual behaviour in Zambia in 2001-02 and in Rwanda in 2005, as well as used data on the HIV serostatus of married or cohabiting couples and non-cohabiting couples that was collected through a voluntary counselling and testing service for urban couples in Lusaka, in Zambia, and Kigali, in Rwanda. They estimated the probability that an individual would acquire an incident HIV infection from a cohabiting or non-cohabiting sexual partner, and then the proportion of total heterosexual HIV transmission which occurs within married or cohabiting couples in these settings each year. DHS data from 1739 Zambian women, 540 Zambian men, 1176 Rwandan women, and 606 Rwandan men was analyzed. Under

the base model, the authors estimated that 55.1% to 92.7% of new heterosexually acquired HIV infections among adults in urban Zambia and Rwanda occurred within serodiscordant marital or cohabiting relationships, depending on the sex of the index partner and on location. Under the extended model, which incorporated the higher rates of reported condom use that were found with non-cohabiting partners, the authors estimated that 60.3% to 94.2% of new heterosexually acquired infections occurred within marriage or cohabitation. An intervention for couples which reduced transmission in serodiscordant urban cohabiting couples from 20% to 7% every year could avert 35.7% to 60.3% of heterosexually transmitted HIV infections that would otherwise occur. Since most heterosexual HIV transmission for both men and women in urban Zambia and Rwanda takes place within marriage or cohabitation, voluntary counselling and testing for couples should be promoted, as should other evidence-based interventions that target heterosexual couples.

**Editors' note: With three-quarters of HIV-infected adults in sub-Saharan Africa unaware of their HIV status and high levels of marital serodiscordance, marriage or cohabitation poses a risk for both men and women. Promoting fidelity for couples without accompanying HIV testing can result in a 20% annual transmission rate. Scale-up of couple-based counselling and testing accompanied by support for marital disclosure and plans for risk reduction, antiretroviral treatment and preventive care for the infected partner, and male circumcision for HIV-negative men is urgently needed.**

#### **4. Sexual transmission and prevention**

van Sighem A, Zhang S, Reiss P, Gras L, van der Ende M, Kroon F, Prins J, de Wolf F; on Behalf of the ATHENA National Observational Cohort Study. Immunologic, Virologic, and Clinical Consequences of Episodes of Transient Viraemia During Suppressive Combination Antiretroviral Therapy. *J Acquir Immune Defic Syndr*. 2008 May 1;48(1):104-8.

van Sighem and colleagues aimed to investigate immunologic, virologic, and clinical consequences of episodes of transient viraemia in patients with sustained virologic suppression. From the AIDS Therapy Evaluation Project, Netherlands cohort, 4447 previously therapy-naive patients were selected who were on continuous combination antiretroviral therapy and had initial success (2 consecutive HIV RNA measurements <50 copies/mL). During episodes of viral suppression (RNA <50 copies/mL), low-level viraemia (RNA 50 to 1000 copies/mL), or high-level viraemia (RNA >1000 copies/mL) after initial success, the occurrence of therapy changes, drug resistance, and clinical events was assessed. During 11,187 person-years of follow-up, 1281 (28.8%) patients had at least 1 RNA measurement >50 copies/mL. Among 8069 episodes, there were 5989 (74.2%) episodes of suppression, 1711 (21.2%) episodes of low-level viraemia, and 369 (4.6%) episodes of high-level viraemia. Most episodes of low-level viraemia consisted of  $\leq 2$  RNA measurements (93.7%), were without clinical events or therapy changes (79.6%), and were without changes in CD4 cell counts. Therapy changes (52.3% of episodes) and resistance (23.3%) were frequently observed during high-level viraemia. In conclusion, episodes of low-level viraemia are frequent and short-lasting, and the low proportion of episodes with clinical events suggests that leaving therapy unchanged is a clinically acceptable strategy. In contrast, high-level viraemia is associated with resistance and is often followed by therapy changes.

**Editors' note: Although the focus here is on whether viraemia should be an indication for a change in therapy, viraemia in previously naive patients on treatment has potential relevance for transmission risk. A high proportion of patients were viraemic during winter when influenza and the common cold are more prevalent, suggesting that**

antigenic stimulation due to other infections may play a role. Thus, although effective antiretroviral treatment reduces viral load, blips can still occur – 28.8% of continuously treated patients in this large-cohort experienced at least one transient episode of viraemia.

Kwara A, Delong A, Rezk N, Hogan J, Burtwell H, Chapman S, Moreira CC, Kurpewski J, Ingersoll J, Caliendo AM, Kashuba A, Cu-Uvin S. Antiretroviral drug concentrations and HIV RNA in the genital tract of HIV-infected women receiving long-term highly active antiretroviral therapy. *Clin Infect Dis*. 2008;46(5):719-25.

Kwara and colleagues aimed to determine antiretroviral drug concentrations and human immunodeficiency virus (HIV) RNA rebound in cervicovaginal fluid in relation to blood plasma in women receiving suppressive highly active antiretroviral therapy. Thirty-four HIV-infected women who had plasma HIV RNA levels < or =80 copies/mL for at least 6 months were enrolled. Sixty-eight paired cervicovaginal fluid and blood plasma drug concentrations and HIV RNA levels were determined before and 3-4 h after drug administration. For each woman and antiretroviral drug, the cervicovaginal fluid:blood plasma drug concentration ratios before and after drug administration were calculated. The nonparametric Wilcoxon rank sum test was used to determine if these ratios were different from 1.0. Lamivudine (administered to 20 patients) and tenofovir (administered to 16) had significantly higher concentrations in cervicovaginal fluid than in blood plasma before drug administration, with mean cervicovaginal fluid:blood plasma concentration ratios of 3.19 (95% confidence interval, 1.2-8.5) and 5.2 (95% confidence interval, 1.2-22.6), respectively. Efavirenz (administered to 13 patients) and lopinavir (administered to 6) had significantly lower concentrations in cervicovaginal fluid, with mean cervicovaginal fluid:blood plasma concentration ratios of 0.01 (95% confidence interval, 0.00-0.03) and 0.03 (0.01-0.11), respectively. During the study visit (median time after enrolment, 6 months), blood plasma and cervicovaginal fluid detectable HIV RNA levels were observed 7 patients (20.6%) and 1 patient (2.9%), respectively. Despite lower cervicovaginal fluid concentrations of key antiretroviral therapy components, such as efavirenz and lopinavir, virologic rebound was rare. The high concentrations of tenofovir and lamivudine in cervicovaginal fluid may have implications for the prevention of sexual transmission during antiretroviral therapy and for pre-exposure or post-exposure prophylaxis. **Editors' note: Both non-nucleoside reverse transcriptase inhibitors and protease inhibitors penetrate poorly into the genital tract achieving concentrations from 3 to 33% of their concentrations in paired blood plasma. Whether this creates the equivalent of local suboptimal therapy which could lead to genital tract viral drug resistance is not known. The good news is that the nucleoside reverse transcriptase inhibitors that form the backbone of combination therapy not only accumulate but actually concentrate in cervicovaginal fluid, which could have implications for prevention of onward HIV transmission.**

Belza MJ, de la Fuente L, Suárez M, Vallejo F, García M, López M, Barrio G, Bolea A; Health And Sexual Behaviour Survey Group. Men who pay for sex in Spain and condom use: prevalence and correlates in a representative sample of the general population. *Sex Transm Infect*. 2008;84:207-211.

Belza and colleagues aimed to estimate the percentage of men who have paid for heterosexual sex in Spain and the percentage who used condoms. They aimed to identify the main factors associated with these behaviours and to describe opinions about condoms. Sexual behaviour probability sample survey in men aged 18-49 years resident in Spain in

2003 (n=5153). Computer-assisted face to face and self interview was used. Bivariate and multivariate logistic regression analyses were performed. 25.4% (n=1306) of the men had paid for heterosexual sex at some time in their lives; 13.3% (n=687) in the last 5 years and 5.7% (n=295) in the last 12 months. In the logistic analysis this behaviour was associated with older age, lower education, being unmarried, foreign birth, being a practicing member of a religious group, unsatisfactory communication with parents about sex, age under 16 years at first sexual intercourse and having been drunk in the last 30 days. Of the men who had paid for sex in the previous 5 years, 95% (n=653) had used a condom in the most recent paid contact. In the multivariate analysis, not using a condom was associated with age over 30 years and first sexual intercourse before age 16 years. Men who did not use condoms in the last commercial intercourse had more negative opinions about condoms. In conclusion, the prevalence of paying for heterosexual sex among Spanish men is the highest ever described in developed countries. The many variables associated with paying for sex and condom use permit the characterisation of male clients of prostitution and should facilitate targeting HIV prevention policies. **Editors' note: There have been many studies of female sex workers but little research on the prevalence of paying for sex in the general male population. This study is intriguing not only because condom use in these encounters is so high but because a quarter of men have paid for sex at some point in their lives. Aside from a number of expected associations, logistical regression found that practicing members of a religious group (94.4% of whom were Catholic) - defined as attending religious services once a week or more - had a higher prevalence of commercial sex relations and were less likely to use condoms in these encounters.**

##### **5. Prevention of mother-to-child transmission**

Pai NP, Barick R, Tulsy JP, Shivkumar PV, Cohan D, Kalantri S, Pai M, Klein MB, Chhabra S. Impact of round-the-clock, rapid oral fluid HIV testing of women in labor in rural India. *PLoS Med.* 2008;5(5):e92.

Testing pregnant women for HIV at the time of labour and delivery is the last opportunity for prevention of mother-to-child HIV transmission measures, particularly in settings where women do not receive adequate antenatal care. However, HIV testing and counselling of pregnant women in labour is a challenge, especially in resource-constrained settings. In India, many rural women present for delivery without any prior antenatal care. Those who do get antenatal care are not always tested for HIV, because of deficiencies in the provision of HIV testing and counselling services. In this context, we investigated the impact of introducing round-the-clock, rapid, point-of-care HIV testing and counselling in a busy labour ward at a tertiary care hospital in rural India. After they provided written informed consent, women admitted to the labour ward of a rural teaching hospital in India were offered two rapid tests on oral fluid and finger-stick specimens (OraQuick Rapid HIV-1/HIV-2 tests, OraSure Technologies). Simultaneously, venous blood was drawn for conventional HIV ELISA testing. Western blot tests were performed for confirmatory testing if women were positive by both rapid tests and dual ELISA, or where test results were discordant. Round-the-clock (24 h, 7 d/wk) abbreviated prepartum and extended postpartum counselling sessions were offered as part of the testing strategy. HIV-positive women were administered prevention of mother-to-child HIV transmission interventions. Of 1,252 eligible women (age range 18 y to 38 y) approached for consent over a 9 month period in 2006, 1,222 (98%) accepted HIV testing in the labour ward. Of these, 1,003 (82%) women presented with either no reports or incomplete reports of prior HIV testing results at the time of admission to the labour ward.

Of 1,222 women, 15 were diagnosed as HIV-positive (on the basis of two rapid tests, dual ELISA and Western blot), yielding a seroprevalence of 1.23% (95% confidence interval [CI] 0.61%-1.8%). Of the 15 HIV test-positive women, four (27%) had presented with reported HIV status, and 11 (73%) new cases of HIV infection were detected due to rapid testing in the labour room. Thus, 11 HIV-positive women received prevention of mother-to-child transmission interventions on account of round-the-clock rapid HIV testing and counselling in the labour room. While both OraQuick tests (oral and finger-stick) were 100% specific, one false-negative result was documented (with both oral fluid and finger-stick specimens). Of the 15 HIV-infected women who delivered, 13 infants were HIV seronegative at birth and at 1 and 4 mo after delivery; two HIV-positive infants died within a month of delivery. In a busy rural labour ward setting in India, Pai and colleagues demonstrated that it is feasible to introduce a program of round-the-clock rapid HIV testing, including prepartum and extended postpartum counselling sessions. Their data suggest that the availability of round-the-clock rapid HIV testing resulted in successful documentation of HIV serostatus in a large proportion (82%) of rural women who were unaware of their HIV status when admitted to the labour room. In addition, 11 (73%) of a total of 15 HIV-positive women received prevention of mother-to-child transmission interventions because of round-the-clock rapid testing in the labour ward. These findings are relevant for prevention of mother-to-child transmission programs in developing countries. **Editors' note: Despite the fact that labour is not an ideal time to make a decision about learning one's serostatus, offering HIV testing during labour is the last chance for women who have had no antenatal care or were not given the opportunity to be tested during pregnancy. Acceptance was high in this study, with HIV prevalence of 1.23% mirroring the 1% anticipated in recent antenatal sentinel surveillance. Studies of cost-effectiveness may be needed to convince policy makers in some resource-constrained settings that this "catch up" approach for women of unknown HIV status has merit.**

## 6. *Sexual and reproductive health*

Watts DH, Park JG, Cohn SE, Yu S, Hitti J, Stek A, Clax PA, Muderspach L, Lertora JJ. Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093. *Contraception*. 2008;77(2):84-90. Epub 2007 Dec 21.

Concomitant use of antiretroviral drugs and hormonal contraceptives may change the metabolism of each and the resulting safety profiles. We evaluated the safety and tolerability of depot medroxyprogesterone acetate among women on antiretroviral drugs. HIV-infected women on selected antiretroviral drug regimens or no antiretroviral drugs were administered medroxyprogesterone acetate 150 mg intramuscularly and evaluated for 12 weeks for adverse events, changes in CD4+ count and HIV RNA levels, and ovulation. Seventy evaluable subjects were included, 16 on nucleoside only or no antiretroviral drugs, 21 on nelfinavir-containing regimens, 17 on efavirenz-containing regimens and 16 on nevirapine-containing regimens. Nine Grade 3 or 4 adverse events occurred in seven subjects; none were judged related to medroxyprogesterone acetate. The most common findings possibly related to medroxyprogesterone acetate were abnormal vaginal bleeding (nine, 12.7%), headache (three, 4.2%), abdominal pain, mood changes, insomnia, anorexia and fatigue, each occurring in two (2.9%) subjects. No significant changes in CD4+ count or HIV RNA levels occurred with DMPA. No evidence of ovulation was detected, and no pregnancies occurred. In conclusion, the clinical profile associated with medroxyprogesterone acetate administration in HIV-infected women, most on antiretroviral drugs, appears similar to that seen in HIV-uninfected

women. medroxyprogesterone acetate prevented ovulation and did not affect CD4+ counts or HIV RNA levels. In concert with previously published medroxyprogesterone acetate/antiretroviral drugs interaction data, these data suggest that medroxyprogesterone acetate can be used safely by HIV-infected women on the antiretroviral drugs studied.

**Editors' note: These results are reassuring, particularly for women on efavirenz, a drug with potential teratogenic effects. However, the number of study participants was small and this was a 12-week study. Long-term DMPA use is associated with increases in weight and fat distribution, which may be exacerbated by some antiretroviral drugs.**

## **7. Health Care delivery**

Unge C, Johansson A, Zachariah R, Some D, Van Engelgem I, Ekstrom AM. Reasons for unsatisfactory acceptance of antiretroviral treatment in the urban Kibera slum, Kenya. *AIDS Care*. 2008;20(2):146-9.

The aim of this study was to explore why patients in the urban Kibera slum, Nairobi, Kenya, offered free antiretroviral treatment at the Médecins Sans Frontières (MSF) clinic, choose not to be treated despite signs of AIDS. Qualitative semi-structured interviews were conducted with 26 patients, 9 men and 17 women. Six main reasons emerged for not accepting antiretroviral treatment: a) fear of taking medication on an empty stomach due to lack of food; b) fear that side-effects associated with antiretroviral treatment would make one more ill; c) fear of disclosure and its possible negative repercussions; d) concern for continuity of treatment and care; e) conflicting information from religious leaders and community, and seeking alternative care (e.g. traditional medicine); f) illiteracy making patients unable to understand the information given by health workers. **Editors' note: The findings of this study guided the following urgent policy changes in the treatment programme: nutritional supplementation with ready-to-use food, adaptation of information pamphlets to local realities, alternative communication methods (peer groups, church, and traditional leaders), voluntary as opposed to mandatory disclosure to a 'treatment buddy', and enhanced links to other community partners in Kibera. Action-oriented research such as this explores problems and their underpinnings to create a platform for reality-based solutions.**

## **8. Genetics**

Phillips EJ, Mallal SA. Pharmacogenetics and the potential for the individualization of antiretroviral therapy. *Curr Opin Infect Dis*. 2008;21(1):16-24.

Genetic associations highlighting differences in the response to HIV infection and treatment have significantly furthered our understanding of the pathogenesis, pharmacokinetics and pharmacodynamics of antiretroviral drug action and toxicities and HIV disease itself. This review focuses on the current knowledge of associations between polymorphisms and treatment outcomes in HIV with particular emphasis on clinically relevant relationships likely to lead to the individualization of antiretroviral therapy. Our understanding of the immunogenetic basis of drug toxicity has been furthered by human leukocyte antigen associations with hypersensitivities for the antiretroviral drugs abacavir and nevirapine. For abacavir in particular, the use of HLA-B\*5701 as a screening test appears to be generalizable across racially diverse populations and has been supported by both observational, and blinded randomized controlled trials. Differences in HIV acquisition and progression as well as antiretroviral efficacy and toxicity will continue to provide the basis for research to define the genetic basis of such diversity. Despite the plethora of research

in this area, numerous barriers exist to the successful operationalization of genetic testing to the clinic. HLA-B\*5701 screening to prevent abacavir hypersensitivity is currently the most relevant to clinical practice and highlights that the promise of cost-effective testing can be facilitated by robust laboratory methodology and quality assurance programs that can be applied to diverse treatment settings. **Editors' note: Drug hypersensitivity syndromes are not directly related to the dose of a drug but are thought to be related to a combination of factors and associated with specific human leukocyte antigen (HLA) alleles within the major histocompatibility complex. In the case of patients starting nevirapine, 16% develop rash, 5% have hypersensitivity reactions with fever and hepatitis, and 0.3% can have severe skin syndromes. Knowledge of HIV pharmacogenetics is growing but unfortunately it will be some time before antiretroviral treatment in the real world can be tailored to patient genetics to avoid hypersensitivity reactions.**

Cossarizza A. Apoptosis and HIV infection: about molecules and genes. *Curr Pharm Des.* 2008;14(3):237-44.

During the evolution, the immune system has developed several strategies to fight viral infections. Apoptosis, autophagy and necrosis are different types of cell death that play a main role in the interactions between infective agents and the host, since they are often important defence mechanisms that have to avoid the spreading of the infection. In turn, viruses have evolved numerous ways to evade the host immune system by influencing the behaviour and functionality of several components. HIV infects and kills CD4+ T helper lymphocytes, preferentially those that are antigen-specific, but also encodes proteins with apoptotic capacities, including gp120, gp160, Tat, Nef, Vpr, Vpu, Vif and, last but not least, the viral protease. This latter protein can kill infected and uninfected lymphocytes through the action of several host molecules, mainly members of the tumour necrosis factor family, or via the mitochondrial apoptotic pathway. The proinflammatory state that is characteristic of both the acute and chronic phase of HIV infection facilitates cell death, and is an additional cause of immune damage. Potent antiretroviral drugs that are largely used in therapy can reduce apoptosis by different mechanisms, that not only include the diminished production of the virus by infected cells and the subsequent reduction of inflammation, but also a direct action on the viral protease. The role of the host genetic background is finally crucial in understanding the process of cell death in HIV infection. **Editors' note: Programmed cell death or apoptosis is one of our most ancestral and potent cell defence mechanisms. HIV manipulates the apoptotic machinery to its advantage. For example, some viral proteins cause down-regulation of CD4 preventing gp120-CD4-mediated cell death. If HIV caused massive cell death, it couldn't survive itself. On our side, we trigger activation of non-infected cells to help cope with the virus but then these innocent bystanders are induced to die by the virus. Research on immunogenetics can provide insights into why some people control HIV better, which may help with the design of antiretroviral therapy for immune reconstitution.**

## 9. Treatment and care

Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, Holmberg SD, Brooks JT; Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med.* 2008;148(10):728-36.

Persons who are HIV-infected may be at higher risk for certain types of cancer than the general population. Patel and colleagues conducted prospective observational cohort studies in the United States to compare cancer incidence among HIV-infected persons with incidence in the general population from 1992 to 2003. 54,780 HIV-infected persons in the Adult and Adolescent Spectrum of HIV Disease Project (47,832 patients) and the HIV Outpatient Study (6948 patients), who contributed 157,819 person-years of follow-up from 1992 to 2003, and 334,802,121 records from the Surveillance, Epidemiology, and End Results program of 13 geographically defined, population-based, central cancer registries were included. Standardized rate ratios were estimated to compare cancer incidence in the HIV-infected population with standardized cancer incidence in the general population. The incidence of the following types of non-AIDS-defining cancer was significantly higher in the HIV-infected population than in the general population: anal (standardized rate ratio, 42.9 [95% CI, 34.1 to 53.3]), vaginal (21.0 [CI, 11.2 to 35.9]), Hodgkin lymphoma (14.7 [CI, 11.6 to 18.2]), liver (7.7 [CI, 5.7 to 10.1]), lung (3.3 [CI, 2.8 to 3.9]), melanoma (2.6 [CI, 1.9 to 3.6]), oropharyngeal (2.6 [CI, 1.9 to 3.4]), leukaemia (2.5 [CI, 1.6 to 3.8]), colorectal (2.3 [CI, 1.8 to 2.9]), and renal (1.8 [CI, 1.1 to 2.7]). The incidence of prostate cancer was significantly lower among HIV-infected persons than the general population (standardized rate ratio, 0.6 [CI, 0.4 to 0.8]). Only the relative incidence of anal cancer increased over time. A study limitation was the lower ascertainment of cancer in the HIV cohorts which may result in a potential bias to underestimate rate disparities. Tobacco use as a risk factor and the effect of changes in cancer screening practices could not be evaluated. In conclusion, the incidence of many types of non-AIDS-defining cancer was higher among HIV-infected persons than among the general population from 1992 to 2003. **Editors' note: In addition to the significantly higher incidence of several types of cancer in people living with HIV compared to the general population, this study found increasing incidence rates over time for melanoma; Hodgkin lymphoma; and colorectal, anal, and prostate cancer, despite the advent of antiretroviral treatment. Both behavioural/lifestyle factors and other viruses (human papilloma virus, Epstein Barr Virus) may be implicated. In the case of HPV infection, prevention includes screening for early detection and treatment, along with evaluation of primary prevention measures such as vaccination and male circumcision.**

## 10. Basic Science

Streeck H, Brumme ZL, Anastario M, Cohen KW, Jolin JS, Meier A, Brumme CJ, Rosenberg ES, Alter G, Allen TM, Walker BD, Altfeld M. Antigen load and viral sequence diversification determine the functional profile of HIV-1-specific CD8+ T cells. *PLoS Med.* 2008;5(5):e100.

Virus-specific CD8(+) T lymphocytes play a key role in the initial reduction of peak viremia during acute viral infections, but display signs of increasing dysfunction and exhaustion under conditions of chronic antigen persistence. It has been suggested that virus-specific CD8(+) T cells with a "polyfunctional" profile, defined by the capacity to secrete multiple cytokines or chemokines, are most competent in controlling viral replication in chronic HIV-1 infection. Streeck and colleagues used HIV-1 infection as a model of chronic persistent viral infection to investigate the process of exhaustion and dysfunction of virus-specific CD8(+) T cell responses on the single-epitope level over time, starting in primary HIV-1 infection. They longitudinally analyzed the polyfunctional epitope-specific CD8(+) T cell responses of 18 patients during primary HIV-1 infection before and after therapy initiation or sequence variation in the targeted epitope. Epitope-specific CD8(+) T cells responded with multiple effector functions to antigenic stimulation during primary HIV-1 infection, but lost their

polyfunctional capacity in response to antigen and up-regulated programmed death 1 (PD-1) expression with persistent viremic infection. This exhausted phenotype significantly decreased upon removal of stimulation by antigen, either in response to antiretroviral therapy or by reduction of epitope-specific antigen load in the presence of ongoing viral replication, as a consequence of in vivo selection of cytotoxic T lymphocyte escape mutations in the respective epitopes. Monofunctionality increased in CD8(+) T cell responses directed against conserved epitopes from 49% (95% confidence interval 27%-72%) to 76% (56%-95%) (standard deviation [SD] of the effect size 0.71), while monofunctionality remained stable or slightly decreased for responses directed against escaped epitopes from 61% (47%-75%) to 56% (42%-70%) (SD of the effect size 0.18) ( $p < 0.05$ ). In conclusion, the data suggest that persistence of antigen can be the cause, rather than the consequence, of the functional impairment of virus-specific T cell responses observed during chronic HIV-1 infection, and underscore the importance of evaluating autologous viral sequences in studies aimed at investigating the relationship between virus-specific immunity and associated pathogenesis. **Editors' note: Polyfunctional CD8<sup>+</sup> T cells that release multiple cytokines in response to antigen are essential to effective immune responses. This study found that these cells lose their polyfunctionality and are exhausted in the face of persistent viral infection. Antiretroviral treatment reduces the amount of antigen in patients and reverses the T-cell exhaustion. The Short Pulse Antiretroviral Therapy at HIV Seroconversion (SPARTAC) international trial is assessing whether early treatment can be beneficial and there are hopes that eventually therapeutic vaccination can lead to restoration of a broad and fully functional cytotoxic lymphocyte immune response.**

That was *HIV This Week*, signing off.

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