

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

Welcome to the 75<sup>th</sup> issue of **HIV This Week**! In this issue, we cover these topics:

### **1. Blood safety**

- How far away are we from the goal of quality assured HIV screening of every unit of blood?

### **2. National responses - injecting drug use**

- Urgent need for scaled-up harm reduction in South-East Asian countries – everyone knows what needs doing so where is the pragmatic leadership?

### **3. Gender and access to treatment**

- How concepts of masculinity trap men and prevent them from accessing treatment and why women can access care much more readily in Burkina Faso

### **4. Male circumcision**

- Foreskin surface area (size) really does matter!
- Does circumcision protect primarily insertive Australian men who have sex with men?

### **5. Monitoring and Evaluation**

- What's in place now to track our progress to reaching Millennium Development Goal 6 to halt and reverse the HIV epidemic in 2015?

### **6. Stigma**

- “Just like fever” and other evidence of antiretroviral treatment-induced normalisation of HIV versus stigma in rural Tanzania

### **7. Microbicides**

- CCR5 inhibitor Maraviroc concentrates right where we need it in cervicovaginal fluid and vaginal tissue
- Intravaginal rings deliver the NNRTI dapivirine throughout the lower female genital tract for a month – time to take this promising prevention modality for women through to trials!

### **8. Policy and economics**

- In the lead up to Copenhagen, lessons from climate change research suggest that HIV research should be more proactive and forward-looking
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- Saving money with pooled viral load testing to pick up treatment failure

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- Repeated low dose mucosal SHIV challenge reveals effective, low-titre antibody protection in macaques – time to recreate human HIV sexual exposure levels in monkeys rather than blasting away with super challenges
- Why you might eventually consider a nasal vaccination

### **11. Basic Science**

- What happens to B cells, the ones that make antibodies, in acute HIV infection?

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- Why acyclovir should be included in syndromic management for genital ulcers in men living with HIV

### **13. Tuberculosis**

- Let's get on with isoniazid preventive therapy for people living with HIV with close monitoring and operational research to improve implementation

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Don't forget that you can find a wealth of information on the HIV epidemic and responses to it at [www.unaids.org](http://www.unaids.org).

## 1. Blood safety

### Progress in Global Blood Safety for HIV

Takei T, Abu Amin N, Schmid G, Dhingra-Kumar N, and Rugg D, *J Acquir Immune Defic Syndr*, 2009;52(S2)

The aim of the report was to assess progress towards ensuring a globally safe blood supply. The authors examined 2 global databases for blood safety: that of the United Nations General Assembly Special Session on HIV/AIDS (UNGASS) blood safety indicator; and that of the Global Database on Blood Safety (GDBS), a database developed by the World Health Organization. The UNGASS data were collected through the Ministry of Health based on the GDBS data, followed by a reconciliation and cross-checking of the data by World Health Organization and United Nations Programme on AIDS (UNAIDS). They found that the proportion of United Nations member countries reporting UNGASS data for blood safety is **among the highest of all UNGASS indicators: 147 of 192 United Nations Member States participated in UNGASS reporting in 2008 and 125 of them (85%) submitted data on blood safety.** Ninety-one of the 125 countries (73%) reported that 100% of collected blood units were screened in a quality assured manner, but 34 countries did not screen all collected blood units in accordance with minimum quality standards. GDBS data showed that 80.7 million blood units were collected globally in 167 countries during 2004–2005, of which 77.3 million were tested for HIV and at least 0.6 million of the remaining 3.4 million donations went untested. In conclusion, progress has been made toward eliminating blood transfusion as a significant cause of HIV infection globally. **Screening all donated blood for HIV in accordance with minimum quality standards** remains vital, however, as health care systems should, at a minimum, do no harm. This **goal is achievable** and would assist in reaching Millennium Development Goals by 2015.

For full text access click here:

<http://journals.lww.com/jaids/toc/2009/12012>

**Editors' note:** Because receiving HIV-infected blood leads to HIV infection in 95 to 100 per cent of people who are transfused with it, ensuring the safety of blood transfusion is a highly cost-effective prevention measure at an estimated 18\$ per HIV infection averted. The fact that screening all donated blood in accordance with standardised procedures in a quality assured manner is still not universal around the world is disturbing. Gaps in blood supply in some settings are endangering lives and 50% of transfusions are unnecessary in others, but it is of immediate concern that so many countries are failing to ensure safe blood for their citizens when they are in dire need. Achieving this goal is not beyond reach and will save lives.

## 2. National responses - injecting drug use

### A situation update on HIV epidemics among people who inject drugs and national responses in South-East Asia Region.

Sharma M, Oppenheimer E, Saidel T, Loo V, Garg R. *AIDS*. 2009;23:1405-13.

The authors explore the magnitude of and current trends in HIV infection among people who inject drugs and estimate the reach of harm reduction interventions among them in seven high-burden countries of the South-East Asia Region. Their **data are drawn from the published and unpublished literature, routine national HIV serological and behavioural surveillance surveys and information from key informants.** Six countries (Thailand, Myanmar, Nepal, Indonesia, India, and Bangladesh) had significant epidemics of HIV among people who inject drugs. In **Thailand, Indonesia, Bangladesh, Myanmar and India, there is no significant decline in the prevalence of HIV epidemics in this population.** In **Nepal, north-east India, and some cities in Myanmar,** there is **some evidence of decline in risk behaviours** and a

**concomitant decline in HIV prevalence.** This is countered by the **rapid emergence of epidemics in new geographical pockets.** Available programme data suggest that less than 12 000 of the estimated 800 000 **(1.5%) people who inject drugs have access to opioid substitution therapy,** and **20-25% were reached by needle-syringe programmes at least once during the past 12 months.** A mapping of harm reduction interventions suggests a lack of congruence between the location of established and emerging epidemics and the availability of scaled-up prevention services. **Harm reduction interventions in closed settings are almost nonexistent.** To achieve significant impact on the HIV epidemics among this population, governments, specifically national AIDS programmes, urgently need to scale up needle-syringe programmes and opioid substitution therapy and make these widely available both in community and closed settings.

**For access to abstract click here:**

<http://www.ncbi.nlm.nih.gov/pubmed/19579290>

**Editors' note:** This broad mapping, across 7 high drug use burden South East Asian countries with significant, longstanding HIV epidemics among people who inject drugs, draws from a variety of data sources to paint a picture of national prevention responses. In addition to the strikingly inadequate reach of harm reduction programmes, current surveillance systems are not designed to pick up new epidemics. Indonesia is the only country with a national strategy (2005-2009) to guide HIV prevention, treatment, and care in prison settings – the very settings that are known to be high-risk environments worldwide for HIV transmission. Methadone and buprenorphine are unavailable and too expensive in most countries. Tensions between supply/demand reduction and harm reduction approaches call out now for enlightened leadership at all levels to implement effective HIV prevention programmes to cover at least 50-60% of people who inject drugs.

### **3. Gender and access to treatment**

#### **Gender asymmetry in healthcare-facility attendance of people living with HIV/AIDS in Burkina Faso.**

*Bila B, Egrot M. Soc Sci Med. 2009; 69:854-61*

Anthropological research in Burkina Faso indicates that more HIV-positive women than HIV-positive men are attending care facilities for people living with HIV and accessing antiretroviral medicine. This article, situated in the field of study of interactions between gender and AIDS, offers a description of this asymmetry and an anthropological analysis of the socio-cultural determinants, through analysis of data from ethnographic research among people living with HIV and health actors. Examining **social representations of femininity and masculinity in Burkinabe society** and the organisation of the healthcare system in connection with gender shed light on the **decision-making processes of both sexes around therapeutic choices and the itinerary of care.** On the one hand, the social values attached to femininity, maternity and the status of wife create conditions for women that favour their attendance at care facilities for people living with HIV and encourage a widespread practice where wives take the place of their husbands in healthcare queues. Moreover, health policies and the effects of women's empowerment within the healthcare system strengthen women's access to health services. On the other hand, **representations of masculinity are fully implicated in the cultural construction of men's reluctance to attend care facilities for people living with HIV.** The **values associated with this masculinity cause men to run great health, economic and social risks,** not only **for themselves,** but also **for their wives and children.** By better understanding the interaction between gender, the experience of HIV and the institutional organisation of healthcare, we can identify ways to reduce men's reluctance to attend care facilities for people living with HIV and improve both prevention and treatment-oriented programmes.

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[http://www.sciencedirect.com/science?\\_ob=ArticleURL&\\_udi=B6VBF-4WJC5WH-2&\\_user=3824252&\\_rdoc=1&\\_fmt=&\\_orig=search&\\_sort=d&\\_docanchor=&view=c&\\_acct=C000055308&\\_version=1&\\_urlVersion=0&\\_userid=3824252&md5=3cd5b502e3ddcd0106a3c8cc3c5cbac6](http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VBF-4WJC5WH-2&_user=3824252&_rdoc=1&_fmt=&_orig=search&_sort=d&_docanchor=&view=c&_acct=C000055308&_version=1&_urlVersion=0&_userid=3824252&md5=3cd5b502e3ddcd0106a3c8cc3c5cbac6)

**Editors' note:** This thoughtful article is an interesting read. Although the effects of gendered systems in sub-Saharan Africa create socioeconomic disadvantage and vulnerability for women compared to men, men are caught up in representations of masculinity that do not allow them to overcome their feelings of shame to seek care. These feelings centre both on having HIV infection and on needing external support for food, medicine and school supplies. In contrast, women's feelings of obligation to be in good health so as to care for their children now and over the long-term motivate them to seek treatment, food, and school supply support readily at health care facilities. The result is that 2 men are followed clinically for every 3 to 6 women despite equivalent HIV prevalence. The solution is not separate service provision, although food support could be accessed at non-HIV care settings using vouchers, and is likely multi-faceted. Awareness raising focused on encouraging men living with HIV to value their social responsibility to their families and seek care might be a good start.

#### 4. Male circumcision

##### Foreskin surface area and HIV acquisition in Rakai, Uganda (size matters).

*Kigozi G, Wawer M, Ssettuba A, Kagaayi J, Nalugoda F, Watya S, Mangan FW, Kiwanuka N, Bacon MC, Lutalo T, Serwadda D, Gray RH. AIDS. 2009; 23:2209-13.*

Male circumcision reduces HIV acquisition in men. The authors assessed whether foreskin surface area was associated with HIV acquisition prior to circumcision. In two randomized trials of male circumcision, the surface area of the foreskin was measured after surgery using standardized procedures. Nine hundred and sixty-five initially HIV-negative men were enrolled in a community cohort who subsequently enrolled in the male circumcision trials, provided 3920.8 person-years of observation prior to circumcision. They **estimated HIV incidence per 100 person-years prior to circumcision, associated with foreskin surface area** categorized into quartiles. **Mean foreskin surface area was significantly higher among men who acquired HIV** (43.3 cm<sup>2</sup>, standard error 2.1) compared with men who remained uninfected (36.8 cm, standard error 0.5, P = 0.01). HIV incidence was 0.80/100 person-years (8/994.9 person-years) for men with foreskin surface areas in the lowest quartile (< or =26.3 cm<sup>2</sup>), 0.92/100 person-years (9/975.3 person-years) with foreskin areas in the second quartile (26.4-35.0 cm<sup>2</sup>), 0.90/100 person-years (8/888.5 person-years) with foreskin area in the third quartile (35.2-45.5 cm<sup>2</sup>) and 2.48/100 person-years (23/926.8 person-years) in men with foreskin surfaces areas in the highest quartile (>45.6 cm<sup>2</sup>). **Compared with men with foreskin surface areas in the lowest quartile, the adjusted incidence rate ratio of HIV acquisition was 2.37** (95% confidence interval 1.05-5.31) **in men with the largest quartile of foreskin surface area.** The risk of male HIV acquisition is increased among men with larger foreskin surface areas.

For access to abstract click here:

[http://www.ncbi.nlm.nih.gov/pubmed/19770623?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_Res ultsPanel.Pubmed\\_RVDocSum&ordinalpos=3](http://www.ncbi.nlm.nih.gov/pubmed/19770623?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_Res ultsPanel.Pubmed_RVDocSum&ordinalpos=3)

**Editors' note:** This retrospective cohort study is the first study examining the association between foreskin surface area and risk of HIV acquisition – and its findings are biologically plausible. Removing the foreskin reduces the risk of HIV acquisition by 50 to 60% because the only remaining unkeratinized mucosa on the penis after circumcision is the urethral meatus (opening). Before circumcision, more foreskin means more HIV target cells in the inner mucosa of the prepuce exposed to vaginal fluids during sex, likely more of the traumatic micro lesions that are open doors for HIV, and more genital ulcers that have welcoming mats out for HIV. In this study, risk of HIV acquisition in men with the largest foreskins was more than twice that of those with the

smallest, leading to the claim that size matters. The larger your foreskin, the more you should think about getting it removed if you might be exposed to HIV now or later.

### **Circumcision and risk of HIV infection in Australian homosexual men.**

*Templeton DJ, Jin F, Mao L, Prestage GP, Donovan B, Imrie J, Kippax S, Kaldor JM, Grulich AE. AIDS. 2009;23:2347-51.*

The aim of the study was to assess circumcision status as a risk factor for HIV seroconversion in homosexual men. The Health in Men (HIM) study was a prospective cohort of homosexual men in Sydney, Australia. HIV-negative men (n = 1426) were recruited primarily from community-based sources between 2001 and 2004 and followed to mid-2007. Participants underwent annual HIV testing, and detailed information on sexual risk behaviour was collected every 6 months. The main outcome measure was HIV incidence in circumcised compared with uncircumcised participants, stratified by whether or not men predominantly practised the insertive role in anal intercourse. There were **53 HIV seroconversions** during follow-up; an **incidence of 0.78 per 100 person-years**. On multivariate analysis controlling for behavioural risk factors, being circumcised was associated with a nonsignificant reduction in risk of HIV seroconversion [hazard ratio 0.78, 95% confidence interval (CI) 0.42-1.45, P = 0.424]. **Among one-third of study participants who reported a preference for the insertive role in anal intercourse, being circumcised was associated with a significant reduction in HIV incidence after controlling for age and unprotected anal intercourse (UAI)** (hazard ratio 0.11, 95% CI 0.03-0.80, P = 0.041). Those who reported a preference for the insertive role overwhelmingly practised insertive rather than receptive UAI. Overall, circumcision did not significantly reduce the risk of HIV infection in the Health in Men cohort. However, it was associated with a significant reduction in HIV incidence among those participants who reported a preference for the insertive role in anal intercourse. Circumcision may have a role as an HIV prevention intervention in this subset of homosexual men.

**For access to abstract click here:**

[http://www.ncbi.nlm.nih.gov/pubmed/19752714?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=3](http://www.ncbi.nlm.nih.gov/pubmed/19752714?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=3)

**Editors' note:** With strategic positioning among gay men on the rise in Australia and the USA (HIV-negative men adopting the insertive role in unprotected anal sex to reduce their risk with HIV-positive partners or those of unknown status), there is increasing interest in the possible protection that male circumcision may provide to primarily insertive men who have sex with men. This first prospective study, following on mixed findings from cross-sectional studies, included systematic validation of circumcision status in a sub-group of participants to assess validity of self-report. Despite lowered study power (only 33% of person-years of exposure were in men with a preference for the insertive role), circumcised men with this preference had significantly reduced HIV incidence. Only randomised controlled trials recruiting uncircumcised men who have sex with men and who predominantly or exclusively practise insertive anal sex in high HIV incidence settings will answer once and for all the question of whether male circumcision reduces the risk of HIV acquisition for primarily insertive men who have sex with men as it does for men who have sex with women.

## **5. Monitoring and Evaluation**

### **Are We on Course for Reporting on the Millennium Development Goals in 2015?**

*Rugg D, Marais H, Law BA, Carael M, De Lay P, and, Warner-Smith M. J Acquir Immune Defic Syndr. 2009;52(S2)*

At the 2001 United Nations General Assembly Special Session on HIV/AIDS (UNGASS), Member States agreed to regularly review progress made in national responses to HIV. This article provides a brief overview of how the resultant global UNGASS reporting system was developed;

the origins, background, limitations and potential of that system; an overview of the articles in this supplement; and crosscutting institutional and methodological issues. The United Nations Member States biennially provide The Joint United Nations Programme on HIV/AIDS (UNAIDS) with data on 25 core indicators of national responses to HIV, collected in Country Progress Reports. This article critically reviews and interprets these data in light of international political considerations and overall data needs. There has been a **considerable improvement in response rates, accompanied by an increase in data quality and completeness**. Both nationally and internationally, the UNGASS process is viewed as being more substantial and important than a reporting exercise to the United Nations General Assembly. **The process has catalyzed the development of national monitoring systems** and has **created opportunities for civil society to monitor and challenge government commitments and deeds**. Although the UNGASS global reporting system now comprises an unequalled wealth of data on HIV responses, collected from a broad range of countries, it cannot yet answer several critical questions about the progress and effectiveness of those responses. **Evaluation studies that go beyond indicator monitoring are needed**, but they will take time to design, fund, implement and interpret. In the meantime, this global monitoring system provides a good indication of the overall progress in the global response to HIV and whether Millennium Development Goal (MDG) 6 (to halt and reverse the HIV epidemic) is likely to be reached by 2015.

**For full text access click here:**

<http://journals.lww.com/jaids/toc/2009/12012>

**Editors' note:** Providing an overview of the monitoring effort underway to track progress toward achieving the 2001 UNGASS Declaration of Commitment, Universal Access by 2010, and Millennium Development Goal 6 by 2015, this article sets the stage for 10 accompanying related papers. There has been significant progress in harmonising indicators and reporting schedules, and strengthening rather than bypassing or overburdening domestic monitoring systems and capacities. However, tensions between, on the one hand, the need for locally useful data to inform programming decisions and improve accountability toward beneficiaries and, on the other hand, the need for data to meet national and international reporting requirements should be acknowledged and addressed. Effective implementation of evidence-informed appropriate HIV prevention, treatment, care and support programmes at scale, with feedback loops to improve quality and outputs, will translate into fewer HIV infections and longer, more productive lives for people living with HIV. Monitoring and evaluation play a supportive but essential role in keeping the train on the track.

## 6. Stigma

**“Just like fever”: a qualitative study on the impact of antiretroviral provision on the normalisation of HIV in rural Tanzania and its implications for prevention.**

*Roura M, Wringe A, Busza J, Nhandi B, Mbata D, Zaba B, Urassa M. BMC Int Health Hum Rights. 2009;9:22.*

Once effective therapy for a previously untreatable condition is made available, a normalisation of the disease often occurs. Part of a broader initiative monitoring the implementation of the national antiretroviral therapy programme, this qualitative study investigated the impact of antiretroviral therapy availability on HIV perceptions in a rural ward of North Tanzania and its implications for prevention. A mix of qualitative methods was used including semi-structured interviews with 53 antiretroviral therapy clinic clients and service providers. Four group activities were conducted with persons living with HIV. Data were analyzed using the qualitative software package NVIVO7. People on ART often reported feeling increasingly comfortable with their status reflecting a certain “normalization” of the disease. This was attributed to their **seeing other people affected by HIV, regaining physical health, returning to productive activities** and **receiving emotional support from health service providers**. Overcoming internalised feelings of shame facilitated disclosure of HIV status, helped to sustain treatment, and stimulated voluntary counselling and

testing uptake. However “**blaming**” stigma -where HIV+ people were considered responsible for acquiring a “moral disease” - **persisted in the community and anticipating it was a key barrier to disclosure and voluntary counselling and testing uptake**. Attributing HIV symptoms to witchcraft seemed an effective mechanism to transfer “blame” from the family unit to an external force but could lead to treatment interruption. As long as an HIV diagnosis continues to have moral connotations, a de-stigmatisation of HIV paralleling that occurring with diseases like cancer is unlikely to occur. **Maximizing synergies between HIV treatment and prevention requires an enabling environment for HIV status disclosure, sustaining treatment, and safer sexual behaviours**. Local leaders should be informed and sensitised and communities mobilised to address the blame-dimension of HIV stigma.

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

<http://www.biomedcentral.com/1472-698X/9/22>

**Editor’s note:** These authors differentiate self-stigma (internalised feelings of shame which result from accepting others’ judgements), enacted stigma (discrimination based on blame, fear, or perceived burden) and anticipated stigma (reactions that people expect from others if it were to become known that they are living with HIV). In this study, provision of HIV treatment had a powerful impact reducing self-stigma, which facilitated disclosure and encouragement of others to access voluntary testing and counselling. However, the potential of these effects was eroded by persistent blaming attitudes in this community that then reinforced anticipated stigma and HIV denial. ‘Normalisation’, whereby people living with HIV are progressively integrated into productive and social life, requires opinion leaders to speak out against blame and marginalisation, promote inclusion of people living with HIV, and come forward for HIV testing themselves.

## 7. Microbicides

### **Maraviroc Concentrates in the Cervicovaginal Fluid and Vaginal Tissue of HIV-Negative Women.**

*Dumond JB, Patterson KB, Pecha AL, Werner RE, Andrews E, Damle B, Tressler R, Worsley J, Kashuba AD. J Acquir Immune Defic Syndr. 2009; 51:546-53.*

The authors compared single- and multiple-dose maraviroc exposures in cervicovaginal fluid (CVF) and vaginal tissue (VT) with blood plasma (BP) and quantified maraviroc protein binding in cervicovaginal fluid. In this open-label pharmacokinetic study of 12 HIV-negative women, 7 paired CVF and BP samples were collected over 12 hours after 1 maraviroc dose. Subjects then received maraviroc twice daily for 7 days. After the last dose, subjects underwent cervicovaginal fluid and blood plasma sampling as on day 1, with additional sampling during terminal elimination. Vaginal tissue biopsies were obtained at steady state. Day 1 and day 7 median maraviroc cervicovaginal fluid AUC<sub>tau</sub> were 1.9- and 2.7-fold higher, respectively, than blood plasma. On day 1, 6 of 12 subjects had **detectable maraviroc cervicovaginal fluid concentrations** within 1 hour; **12 of 12 were detectable within 2 hours**, and all exceeded the protein-free IC<sub>90</sub>. On day 7, maraviroc cervicovaginal fluid protein binding was 7.6% and the VT AUC<sub>tau</sub> was 1.9-fold higher than blood plasma. Maraviroc cervicovaginal fluid concentrations 72 hours after dose and blood plasma concentrations 12 hours after dose were similar. **Higher maraviroc exposure in the female genital tract** provides a pharmacologic basis for further evaluation of chemokine receptor 5 antagonists in HIV infection prophylaxis. **This is the first study to report antiretroviral vaginal tissue concentrations, cervicovaginal fluid protein binding, and cervicovaginal fluid terminal elimination.**

[For abstract access click here:](#)

[http://www.ncbi.nlm.nih.gov/pubmed/19546811?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_Res ultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19546811?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_Res ultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**Editors’ note:** Discordance between antiretroviral concentrations in the blood plasma and genital tract compartments may result in ongoing HIV genital shedding in the presence of undetectable

viral load in blood plasma. This has implications for onward HIV transmission and could lead to harbouring of resistant virus which could reseed systemically producing treatment failure. Thus the degree to which antiretroviral drugs concentrate in the genital tract is important both for public health and for individual treatment outcome. Since viruses that use CCR5 chemokine receptors predominate in the early stages of mucosal transmission, this team studied the pharmacokinetics of the CCR5 inhibitor maraviroc in the genital tract. It achieved not only high cervicovaginal fluid concentrations but also high vaginal tissue concentrations – about twice as high as in blood plasma. These results were a surprise because maraviroc has high protein-binding affinity which reduces its activity. Interestingly this study found protein-binding to be 10 times less in the cervicovaginal fluid than in blood plasma, meaning that the drug is active where we need it to be. A number of questions remain unanswered but maraviroc deserves further study for the prevention of heterosexual transmission.

### **Safety and pharmacokinetics of dapivirine delivery from matrix and reservoir intravaginal rings to HIV-negative women.**

Nel A, Smythe S, Young K, Malcolm K, McCoy C, Rosenberg Z, Romano J. *J Acquir Immune Defic Syndr.* 2009; 51:416-23.

Vaginal microbicides for the prevention of HIV transmission may be an important option for protecting women from infection. Incorporation of **dapivirine, a lead candidate nonnucleoside reverse transcriptase inhibitor**, into **intravaginal rings (IVRs) for sustained mucosal delivery may increase microbicide product adherence and efficacy** compared with conventional vaginal formulations. Twenty-four healthy HIV-negative women 18-35 years of age were randomly assigned (1:1:1) to dapivirine matrix intravaginal ring, dapivirine reservoir intravaginal ring, or placebo intravaginal ring. Dapivirine concentrations were measured in plasma and vaginal fluid samples collected at sequential time points over the 33-day study period (28 days of intravaginal ring use, 5 days of follow-up). Safety was assessed by pelvic/colposcopic examinations, clinical laboratory tests, and adverse events. Both intravaginal ring types were safe and well tolerated with similar adverse events observed in the placebo and dapivirine groups. **Dapivirine from both intravaginal ring types was successfully distributed throughout the lower genital tract at concentrations** over 4 logs greater than the EC50 against wild-type HIV-1 (LAI) in MT4 cells. Maximum concentration (Cmax) and area under the concentration-time curve (AUC) values were significantly **higher with the matrix than reservoir intravaginal ring**. Mean plasma concentrations of dapivirine were <2 ng/mL. These findings suggest that intravaginal ring delivery of microbicides is a viable option meriting further study.

For abstract access click here:

[http://www.ncbi.nlm.nih.gov/pubmed/19623693?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19623693?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**Editors' note:** The idea of an intravaginal ring carrying an antiretroviral for HIV prevention and needing replacement once a month or less is attractive. This study found that such rings, carrying the nonnucleoside reverse transcriptase inhibitor dapivirine, were safe, well-tolerated, and produced high levels of dapivirine in cervicovaginal secretions. The rings tested released drug through different mechanisms but pharmacokinetic studies found that systemic exposure of dapivirine in the blood was low with both of them. Now it's on to the next stage!

## **8. Policy and economics**

### **Rethinking the conceptual terrain of AIDS scholarship: lessons from comparing 27 years of AIDS and climate change research.**

Chazan M, Brklacich M, Whiteside A. *Global Health.* 2009;5:12.

While there has recently been significant medical advance in understanding and treating HIV, limitations in understanding the complex social dimensions of HIV epidemics continue to restrict a host of prevention and development efforts from community through to international levels. These gaps are rooted as much in limited conceptual development as they are in a lack of empirical research. In this conceptual article, the authors compare and contrast the evolution of climate change and AIDS research. They demonstrate how scholarship and response in these two seemingly disparate areas share certain **important similarities**, such as the **"globalization" of discourses** and associated **masking of uneven vulnerabilities**, the **tendency toward technofixes**, and the **polarization of debates** within these fields. They also examine key divergences, noting in particular that climate change research has tended to be more forward-looking and longer-term in focus than AIDS scholarship. Suggesting that AIDS scholars can learn from these key parallels and divergences, the paper offers four directions for advancing AIDS research: **focusing more on the differentiation of risk and responsibility within and among AIDS epidemics; taking (back) on board social justice approaches; moving beyond polarized debates; and shifting focus from reactive to forward-looking and proactive approaches.**

For abstract access click here:

[http://www.ncbi.nlm.nih.gov/pubmed/19807923?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19807923?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**Editors' note:** In the lead up to Copenhagen, this article makes for a very stimulating read. You will learn about the similarities and differences between HIV and climate change research but also about how the response to these two threats was conceptualised at different time periods. Both phenomena are complex, unprecedented, and highly dynamic. For both, scholarship has evolved from a physical or life sciences perspective to one that integrates the social sciences. HIV researchers can learn from the forward-looking and longer-term focus of climate change research, along with its well-considered social vulnerability concepts. A strong message emerges: we need to intervene now proactively to identify and address existing context-specific vulnerabilities to HIV infection and AIDS impacts, before HIV epidemics have fully run their course, in order to mitigate future impacts. It means moving away from a crisis footing to a forward-looking proactive stance to understand what is needed now to reduce or prevent future hardships.

### Critical choices in financing the response to the global HIV/AIDS pandemic.

Hecht R, Bollinger L, Stover J, McGreevey W, Muhib F, Madavo CE, de Ferranti D. *Health Aff (Millwood)*. 2009;28:1591-605.

The HIV pandemic will enter its fiftieth year in 2031. Despite much progress, there are thirty-three million infected people worldwide, and 2.3 million adults were newly infected in 2007. Without a change in approach, a major pandemic will still be with us in 2031. Modelling carried out for the AIDS 2031 project suggests that **funding required for developing countries to address the pandemic could reach \$35 billion annually by 2031**-three times the current level. Even then, more than a million people will still be newly infected each year. However, **wise policy choices focusing on high-impact prevention and efficient treatment could cut costs by half.** Investments in new prevention tools and major behaviour-change efforts are needed to spur more rapid advances. Existing donors, middle-income countries with contained epidemics, philanthropists, and innovative financing could help bridge the likely funding gap.

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**Editors' note:** Looking at what might be done differently to alter significantly the course of the HIV pandemic in order to achieve by 2031 few new infections, nearly all those in need of treatment receiving it, and children orphaned by AIDS assisted to lead normal lives, this costs and financing group lays out some stark choices. Modelling of four scenarios – rapid scale-up, current trends, hard choices for prevention, and structural change – reveals that at best 1 million new adult infections will occur in 2031. The 'game-changers', while waiting for a vaccine or cure, are high

reach, effective prevention programmes for people who inject drugs, men who have sex with men, people who sell sexual services, and increasing numbers of discordant couples as the epidemic matures. Anticipating that resource requirements are set to increase rapidly over the next 5 to 8 years, six policy actions are described to expand financing for HIV in low- and middle-income countries. This is a sobering but essential read for us all.

## 9. Diagnosis and monitoring

### **Evaluation of a dried blood spot HIV-1 RNA program for early infant diagnosis and viral load monitoring at rural and remote healthcare facilities.**

Lofgren SM, Morrissey AB, Chevallier CC, Malabeja AI, Edmonds S, Amos B, Sifuna DJ, von Seidlein L, Schimana W, Stevens WS, Bartlett JA, Crump JA. *AIDS*. 2009 23(18):2459-66.

Lofgren and colleagues set out to assess technical and operational performance of a **dried blood spot-based HIV-1 RNA service for remote healthcare facilities** in a low-income country. A method comparison and operational evaluation of dried blood spot RNA against conventional tests for **early infant diagnosis of HIV and HIV RNA quantitation under field conditions in Tanzania** was conducted. Dried blood spots were prepared and plasma was frozen at -80 degrees C. Dried blood spots were mailed and plasma couriered to a central laboratory for testing using the Abbott m2000 system. Infant diagnosis dried blood spots were also tested for HIV-1 DNA by ROCHE COBAS AmpliPrep/COBAS TaqMan System. Results of dried blood spot RNA were compared with conventional tests; program performance was described. Among 176 infant diagnosis participants, using a **threshold of at least 1000 copies/ml, sensitivity and specificity of dried blood spot versus plasma RNA were 1.00 and 0.99, and of dried blood spot RNA versus dried blood spot DNA were 0.97 and 1.00**. Among 137 viral load monitoring participants, when plasma and dried blood spot RNA were compared, r value was 0.9709; r value was 0.9675 for at least 5000 copies/ml but was 0.7301 for less than 5000 copies/ml. The highest plasma RNA value at which dried blood spot RNA was not detected was 2084 copies/ml. **Median (range) turnaround time from sample collection to result receipt at sites was 23 (4-69) days. The Tanzania mail service successfully transmitted all dried blood spot and results between sites and the central laboratory.** Under program conditions in Tanzania, dried blood spot provided HIV-1 RNA results comparable to conventional methods to remote healthcare facilities. The authors propose dried blood spot RNA testing as an alternative to liquid plasma for HIV-1 RNA services in remote areas

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**Editors' note:** In this study, the weekly cost of mailing dried blood spot specimens from healthcare facilities to the central laboratory was 6\$ compared to a weekly ground transport of frozen plasma samples on dry ice of 515\$. The excellent sensitivity and specificity results for paediatric HIV diagnosis reported for dried blood spot specimens here, combined with a reasonable turnaround time for results in the absence of electronic or fax communications, suggests that cost-effectiveness analyses should be quickly undertaken. The earlier that infants with HIV infection are diagnosed, the sooner they can be placed on treatment.

### **The use of pooled viral load testing to identify antiretroviral treatment failure.**

Smith DM, May SJ, Pérez-Santiago J, Strain MC, Ignacio CC, Haubrich RH, Richman DD, Benson CA, Little SJ. *AIDS*. 2009; 23:2151-8.

To develop less costly methods to virologically monitor patients receiving antiretroviral therapy, the authors evaluated methods that use pooled blood samples and quantitative information available from viral load assays to monitor a cohort of patients on first-line antiretroviral therapy for virologic

failure. They evaluated 150 blood samples collected after 6 months of therapy from participants enrolled in a San Diego primary infection program between January 1998 and January 2007. **Samples were screened for virologic failure with individual viral load testing, 10 x 10 matrix pools and minipools of five samples.** For the pooled platforms (matrix and minipools), the authors used a search and retest algorithm based on the quantitative viral load data to resolve samples that remained ambiguous for virologic failure. Viral load thresholds were more than 500 and more than 1500 copies/ml for the matrix and more than 250 and more than 500 copies/ml for the minipool. Efficiency, accuracy and result turnaround times were evaluated. Twenty-three percent of cohort samples were detectable at more than 50 HIV RNA copies/ml. **At an algorithm threshold of more than 500 HIV RNA copies/ml, both minipool and matrix methods used less than half the number of viral load assays to screen the cohort,** compared with testing samples individually. Both pooling platforms had negative predictive values of 100% for viral loads of more than 500 HIV RNA copies/ml and at least 94% for viral loads of more than 250 HIV RNA copies/ml. In this cohort, **both pooling methods improved the efficiency of virologic monitoring over individual testing** with a minimal decrease in accuracy. These methods may allow for the induction and sustainability of the virologic monitoring of patients receiving antiretroviral therapy in resource-limited settings.

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**Editors' note:** Pooling strategies mix 5, 10, or more samples together for testing. If the pool is positive then each sample in the pool is tested to see which one(s) is (are) responsible. Viral load monitoring for patients on antiretroviral treatment is not recommended or performed in most resource-limited settings where the focus has been on getting more people in need on treatment. Adaptation of assays in current clinical use for settings with diverse HIV subtypes would allow the kinds of efficiency gains described here. The objective would be improved clinical outcomes and limits on the development of drug resistance.

## 10. Vaccines

**Effective, low-titre antibody protection against low-dose repeated mucosal SHIV challenge in macaques.**

*Hessell AJ, Poignard P, Hunter M, Hangartner L, Tehrani DM, Bleeker WK, Parren PW, Marx PA, Burton DR. Nat Med. 2009 15(8):951-4.*

Neutralizing antibodies are thought to be crucial for HIV vaccine protection, but studies in animal models suggest that high antibody concentrations are required. This is a major potential hurdle for vaccine design. However, these **studies typically apply a large virus inoculum to ensure infection in control animals in single-challenge experiments. In contrast, most human infection via sexual encounter probably involves repeated exposures to much lower doses of virus.** Therefore, animal studies may have provided an overestimate of the levels of antibodies required for protection in humans. The authors investigated whether plasma concentrations of antibody corresponding to relatively modest neutralization titres in vitro could protect macaques from repeated intravaginal exposure to low doses of a simian immunodeficiency virus-HIV chimera (SHIV) that uses the CC chemokine receptor 5 (CCR5) co-receptor. An effector function-deficient variant of the neutralizing antibody was also included. The results show that a **substantially larger number of challenges is required to infect macaques treated with neutralizing antibody than control antibody-treated macaques,** and support the notion that effector function may contribute to antibody protection. Overall, the results imply that **lower amounts of antibody than previously considered protective may provide benefit in the context of typical human exposure to HIV-1.**

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**Editors' note:** This study, as in virtually all similar studies published to date, used viruses matched to the neutralising antibody tested. Thus, it is unclear whether this strategy would protect against a variety of circulating viruses. Nonetheless, it is tantalising to think that this macaque study using low dose viral challenges that better reflect repeated human mucosal exposure to low numbers of virus particles may in some way help us to understand the results of the RV144 Thai vaccine trial in which low risk participants may have been better protected. We await with anticipation further results of that trial over the coming months.

### **Nasal DNA-MVA SIV vaccination provides more significant protection from progression to AIDS than a similar intramuscular vaccination.**

*Manrique M, Kozlowski P, Wang SW, Wilson R, Micewicz E, Montefiori D, Mansfield K, Carville A, Aldovini A. Mucosal Immunol. 2009; 2:536-50.*

Preventive human immunodeficiency virus (HIV) vaccination may require **induction of virus-specific immune responses at mucosal sites to contain viral infection locally after exposure, as most HIV infections occur through mucosal surfaces.** The authors compared the efficacy of an intranasal or intramuscular Simian immunodeficiency virus (SIV)+ interleukin (IL)-2+IL-15 DNA/SIV-MVA (modified vaccinia virus Ankara) vaccination in preventing disease progression in SIVmac251 intrarectally challenged rhesus macaques. SIV-specific rectal IgA responses were more significantly persistent in nasally vaccinated than in intramuscularly vaccinated animals. No significant differences were observed in the magnitude of systemic T-cell responses between the two groups, although the nasal immunization induced more significant anti-SIV T-cell responses in the colorectal mucosa. After challenge, CD4(+) central memory (C(M)) T-cell preservation and significant disease-delay were observed in both vaccination groups. However, **nasally vaccinated animals had more significant early preservation of circulating and colorectal CD4(+) C(M) T cells, of circulating CD4(+)/alpha4beta7(+) effector memory (E(M)) T cells, and a longer disease-free interval when compared with the intramuscularly vaccinated or control groups.** Regardless of vaccination status, long-term viraemia control and preservation of CD4(+) C(M) T cells was detected in animals with significantly higher systemic CD8(+)/tumour necrosis factor (TNF)-alpha(+) and CD8(+)/interferon (IFN)-gamma(+) T-cell responses and higher SIV-specific CD4(+)/IL-2(+) responses in colorectal T cells.

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**Editors' note:** Can you imagine taking a vaccine nasally? In this study, nasal vaccination provided more significant protection from progression to AIDS than classical intramuscular vaccination. It is possible that different mucosal routes will provide different degrees of protection. One thing to aim for would be lower viral loads in the gut in acute infection so that there would be less antigen driving immune activation, our antibody response to HIV. A vaccine that did not prevent HIV infection but that would delay the onset of disease by limiting viral replication from the start would be a welcome addition.

## **11. Basic Science**

### **Polyclonal B cell differentiation and loss of gastrointestinal tract germinal centers in the earliest stages of HIV-1 infection.**

*Levesque MC, Moody MA, Hwang KK, Marshall DJ, Whitesides JF, Amos JD, Gurley TC, Allgood S, Haynes BB, Vandergrift NA, Plonk S, Parker DC, Cohen MS, Tomaras GD, Goepfert PA, Shaw GM,*

Schmitz JE, Eron JJ, Shaheen NJ, Hicks CB, Liao HX, Markowitz M, Kelsoe G, Margolis DM, Haynes BF. *PLoS Med.* 2009; 6(7):e1000107.

The antibody response to HIV-1 does not appear in the plasma until approximately 2-5 weeks after transmission, and neutralizing antibodies to autologous HIV-1 generally do not become detectable until 12 weeks or more after transmission. Moreover, levels of HIV-1-specific antibodies decline on antiretroviral treatment. The mechanisms of this **delay in the appearance of anti-HIV-1 antibodies and of their subsequent rapid decline** are not known. While the effect of HIV-1 on depletion of gut CD4(+) T cells in acute HIV-1 infection is well described, the authors studied blood and tissue B cells soon after infection to determine the effect of early HIV-1 on these cells. In human participants, they analyzed B cells in blood as early as 17 days after HIV-1 infection, and in terminal ileum inductive and effector microenvironments beginning at 47 days after infection. They found that **HIV-1 infection rapidly induced polyclonal activation and terminal differentiation of B cells in blood and in gut-associated lymphoid tissue (GALT) B cells**. The specificities of antibodies produced by GALT memory B cells in acute HIV-1 infection (AHI) included not only HIV-1-specific antibodies, but also influenza-specific and autoreactive antibodies, indicating very early onset of HIV-1-induced polyclonal B cell activation. **Follicular damage or germinal centre loss in terminal ileum Peyer's patches** was seen with 88% of follicles exhibiting B or T cell apoptosis and follicular lysis. Early induction of polyclonal B cell differentiation, coupled with follicular damage and germinal centre loss soon after HIV-1 infection, may explain both the high rate of decline in HIV-1-induced antibody responses and the delay in plasma antibody responses to HIV-1.

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<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000107>

**Editors' note:** B lymphocytes are born and mature in the bone marrow before they enter the blood stream looking for interesting antigens. Once activated, they change into antibody-secreting cells and memory B lymphocytes that respond quickly to that antigen. The death of infected and uninfected CD4 T cells in the gut in acute infection is well known but less is understood about what happens to B cells and why the antibody response to HIV is so slow. This study demonstrates that Peyer's patch B cells in the gut die massively, with significant germinal centre destruction. How this happens is unclear but we really need to understand how HIV subverts our initial humoral responses in order to know how quickly neutralising antibodies that are pre-primed by a vaccine would have to appear in order to be effective against HIV.

## 12. Sexual transmission

### Improvement in Healing and Reduction in HIV Shedding with Episodic Acyclovir Therapy as Part of Syndromic Management among Men: A Randomized, Controlled Trial.

Paz-Bailey G, Sternberg M, Puren AJ, Markowitz LE, Ballard R, Delany S, Hawkes S, Nwanyanwu O, Ryan C, Lewis DA. *J Infect Dis.* 2009;200:1039-49.

It is uncertain whether episodic acyclovir will enhance ulcer healing if delivered at primary health care settings, because there is often a delay in treatment initiation. A double-blind, randomized, placebo-controlled trial of 5-day acyclovir (400 mg 3 times daily) was conducted among men with genital ulcers in South Africa. Participants received syndromic management; were tested for ulcer aetiology, human immunodeficiency virus (HIV), syphilis, and herpes simplex virus type 2 (HSV-2); and were seen over the course of a month to evaluate ulcer healing and HIV-1 RNA shedding. Outcomes were ulcer duration and HIV-1 RNA shedding, assessed on day 7 among HIV-1-seropositive participants with a herpetic ulcer. A total of **309 men received acyclovir**, and **306 received placebo; 63% were HIV-1 positive**. There were 295 HIV-1-positive participants with a herpetic ulcer. Acyclovir improved ulcer healing-**61% of those receiving acyclovir healed by day 7, compared with 42% of those receiving placebo** (adjusted relative risk, 1.4 [95% confidence interval, 1.1-1.8]). **Acyclovir also improved healing by a median of 3 days** and reduced HIV-1

ulcer shedding on day 7 (24% for acyclovir vs 37% for placebo). The authors report that addition of acyclovir to syndromic management will improve healing of genital ulcers and may potentially reduce HIV transmission in combination with other interventions.

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**Editors' note:** The results of this acyclovir trial for the 63% of participants who were HIV-positive are encouraging – acyclovir healed herpes simplex-2 (HSV-2) ulcers more quickly (median of 3 days) and reduced HIV shedding from the ulcers. The latter could be due in part to the direct effect of acyclovir itself on HIV replication. WHO recommends that countries in which HSV-2 accounts for more than 30% of genital ulcer disease add antiherpetic treatment to syndromic management algorithms for genital ulcer disease. Why this is not uniformly done is unclear – the cost of treatment has been much reduced by generic acyclovir. Even though trials to date have not found that acyclovir reduces ongoing HIV transmission, it provides symptom relief and reduces herpes shedding. Given that the ulcer is often what may have brought the patient in for care, providers should take advantage of the opportunity while prescribing acyclovir to initiate discussions about HIV testing and counselling with all patients presenting with genital ulcer disease – the majority are unlikely unaware of their HIV status and are not accessing HIV prevention and treatment services.

### 13. Tuberculosis

**Isoniazid preventive therapy for people living with HIV: public health challenges and implementation issues.**

*Ait-Khaled N, Alarcon E, Bissell K, Boillot F, Caminero JA, Chiang CY, Clevenbergh P, Dlodlo R, Enarson DA, Enarson P, Ferroussier O, Fujiwara PI, Harries AD, Heldal E, Hinderaker SG, Kim SJ, Lienhardt C, Rieder HL, Rusen ID, Trébucq A, Van Deun A, Wilson N. Int J Tuberc Lung Dis. 2009 ;13:927-35.*

Isoniazid preventive therapy is recognised as an important component of collaborative tuberculosis and human immunodeficiency virus (HIV) activities to reduce the burden of tuberculosis in people living with HIV. However, there has been little in the way of isoniazid preventive therapy implementation at country level. This failure has resulted in a recent call to arms under the banner title of the '**Three I's**' (**infection control** to prevent nosocomial transmission of tuberculosis in health care settings, **intensified tuberculosis case finding** and **isoniazid preventive therapy**). The authors review the background of isoniazid preventive therapy. They discuss the important challenges of isoniazid preventive therapy in people living with HIV, namely responsibility and accountability for the implementation, **identification of latent tuberculosis infection, exclusion of active tuberculosis and prevention of isoniazid resistance, length of treatment and duration of protective efficacy**. The authors also highlight several research questions that currently remain unanswered and offer practical suggestions about how to scale up isoniazid preventive therapy in the field, including the **need to integrate isoniazid preventive therapy into a package of care for people living with HIV**, the setting up of **operational projects with the philosophy of 'learning while doing'**, the **development of flow charts for eligibility for isoniazid preventive therapy**, the development and implementation of **care prior to antiretroviral treatment**, and finally issues around **procurement, distribution, monitoring and evaluation**. The authors support the implementation of isoniazid preventive therapy, but only if it is done in a safe and structured way. There is a definite risk that 'sloppy' isoniazid preventive therapy will be inefficient and, worse, could lead to the development of multidrug-resistant tuberculosis, and this must be avoided at all costs.

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<http://www.ingentaconnect.com/content/iuatld/ijtld/2009/00000013/00000008/art00003>

**Editors' note:** Have you wondered why TB prophylaxis with isoniazid for people living with HIV is not getting the traction it deserves? This clear, straight to the heart of the matter article underscores the challenges of implementing isoniazid preventive therapy (IPT). These include defining clearly who is responsible, determining who should receive it, excluding active TB and preventing isoniazid resistance, and enhancing the duration of protective efficacy. Among the practical suggestions for scaling up IPT is its integration into the package of pre-antiretroviral treatment care. Pre-ART care can include regular checks of clinical status, CD4 counts, cotrimoxazole preventive therapy (CPT), nutritional support or guidance, family planning, counselling and provision of HIV prevention tools, and insecticide treated bed nets to prevent malaria. National AIDS programmes and national TB programmes need to work together to include IPT in pre-ART care and ensure the conduct of quality monitoring and operational research designed to detect and address problems quickly to improve programme performance.

That was *HIV this week*, signing off.

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