Welcome to HIV this month! In this issue, we cover the following topics:

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• Role for LAM test in TB diagnosis among the sickest people living with HIV
• Antiretroviral choice may affect malaria outcomes in children

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UNAIDS
1. HIV testing and treatment

Unintended adverse consequences of electronic health record introduction to a mature universal HIV screening program.


Early HIV detection and treatment decreases morbidity and mortality and reduces high-risk behaviors. Many Emergency Departments (EDs) have HIV screening programs as recommended by the Centers for Disease Control and Prevention. Recent federal legislation includes incentives for electronic health record (EHR) adoption. Our objective was to analyze the impact of conversion to EHR on a mature ED-based HIV screening program. A retrospective pre- and post-EHR implementation cohort study was conducted in a large urban, academic ED. Medical records were reviewed for HIV screening rates from August 2008 through October 2013. On 1 November 2010, a comprehensive EHR system was implemented throughout the hospital. Before EHR implementation, labs were requested by providers by paper orders with HIV-1/2 automatically pre-selected on every form. This universal ordering protocol was not duplicated in the new EHR; rather it required a provider to manually enter the order. Using a chi-squared test, we compared HIV testing in the 6 months before and after EHR implementation; 55 054 patients presented before, and 50 576 after EHR implementation. Age, sex, race, acuity of presenting condition, and HIV seropositivity rates were similar pre- and post-EHR, and there were no major patient or provider changes during this period. Average HIV testing rate was 37.7% of all ED patients pre-, and 22.3% post-EHR, a 41% decline (p < 0.0001), leading to 167 missed new diagnoses after EHR. The rate of HIV screening in the ED decreased after EHR implementation, and could have been improved with more thoughtful inclusion of existing human processes in its design.

Abstract access

Editor’s notes: The introduction of Electronic Health Records is beneficial for sharing patient information between health care providers in large health care settings. However, as the authors of this paper illustrate with this thoughtful case study, the introduction of electronic health records in some settings may worsen rather than improve care. In this case, the electronic health record system which was introduced did not faithfully mimic the manual system it replaced. HIV-screening which had previously been an ‘opt out’ option for laboratory testing, became an ‘opt-in’ option in the new system. As a result, testing rates went down. Interestingly, a similar electronic system was introduced in another hospital nearby. The effect on testing rates was noticed there and a manual workaround put in place. The nursing director in that institution ‘was a very strong personal advocate and champion for the HIV screening programme there’. The authors point to the importance of testing new systems carefully and checking for unintended consequences on patient care.

The PHACS SMARTT Study: assessment of the safety of in utero exposure to antiretroviral drugs.


The Surveillance Monitoring for ART Toxicities (SMARTT) cohort of the Pediatric HIV/AIDS Cohort Study includes over 3500 HIV-exposed but uninfected infants and children at 22 sites in the US, including Puerto Rico. The goal of the study is to determine the safety of in utero
exposure to antiretrovirals (ARVs) and to estimate the incidence of adverse events. Domains being assessed include metabolic, growth and development, cardiac, neurological, neurodevelopmental (ND), behavior, language, and hearing. SMARTT employs an innovative trigger-based design as an efficient means to identify and evaluate adverse events. Participants who met a predefined clinical or laboratory threshold (trigger) undergo additional evaluations to define their case status. After adjusting for birth cohort and other factors, there was no significant increase in the likelihood of meeting overall case status (case in any domain) with exposure to combination ARVs (cARVs), any ARV class, or any specific ARV. However, several individual ARVs were significantly associated with case status in individual domains, including zidovudine for a metabolic case, first trimester stavudine for a language case, and didanosine plus stavudine for a ND case. We found an increased rate of preterm birth with first trimester exposure to protease inhibitor-based cARV. Although there was no overall increase in congenital anomalies with first trimester cARV, a significant increase was seen with exposure to atazanavir, ritonavir, and didanosine plus stavudine. Tenofovir exposure was associated with significantly lower mean whole-body bone mineral content in the newborn period and a lower length and head circumference at 1 year of age. With ND testing at 1 year of age, specific ARVs (atazanavir, ritonavir-boosted lopinavir, nelfinavir, and tenofovir) were associated with lower performance, although all groups were within the normal range. No ARVs or classes were associated with lower performance between 5 and 13 years of age. Atazanavir and saquinavir exposure were associated with late language emergence at 1 year, but not at 2 years of age. The results of the SMARTT study are generally reassuring, with little evidence for serious adverse events resulting from in utero ARV exposure. However, several findings of concern warrant further evaluation, and new ARVs used in pregnancy need to be evaluated.

Abstract Full-text [free] access

Editor's notes: The SMARTT study set out to determine the safety of in utero exposure to antiretroviral (ARV) therapy using a trigger-based surveillance design to identify adverse events in a cohort of HIV-positive mothers and their HIV-exposed but HIV-negative children in the United States of America and Puerto Rico. A ‘trigger’ was set off if participants met a predefined clinical or laboratory threshold, with additional specified evaluations to determine if they met a predefined adverse event “case” definition. After adjusting for birth cohort and other factors, there was no significant increase in the likelihood of meeting overall case status (case in any domain, such as growth and development or language etc.) with exposure to combination ARVs or any ARV class. No single ARV prophylaxis was associated with an increased risk of overall case status on adjusted analysis. However, several ARVs had significant associations in unadjusted analysis, namely between (1) maternal PI-based ARV prophylaxis during pregnancy and premature delivery and low birth weight; and (2) exposure to atazanavir and a twofold-higher risk of congenital anomalies. Overall the results from this study are reassuring, but some of the findings warrant further evaluation.

Chronic morbidity among older children and adolescents at diagnosis of HIV infection.


Background: Substantial numbers of children with HIV present to health care services in older childhood and adolescence, previously undiagnosed. These “slow-progressors” may experience
considerable chronic ill-health, which is not well-characterised. We investigated the prevalence of chronic morbidity among children aged 6-15 years at diagnosis of HIV infection.

Methods: A cross sectional study was performed at seven primary care clinics in Harare, Zimbabwe. Children aged 6-15 years who tested HIV positive following provider-initiated HIV testing and counselling were recruited. A detailed clinical history and standardised clinical examination was undertaken. The association between chronic disease and CD4 count was investigated using multivariate logistic regression.

Results: Of the 385 participants recruited (52% female, median age 11 years (IQR 8-13)), 95% were perinatally HIV-infected. The median CD4 count was 375 (IQR 215-599) cells/mm$^3$. Although 78% had previous contact with health care services, HIV testing had not been performed. There was a high burden of chronic morbidity: 23% were stunted, 21% had pubertal delay, 25% had chronic skin disease, 54% had a chronic cough of more than 1 month's duration, 28% had abnormal lung function and 12% reported hearing impairment. There was no association between CD4 count of <500 cells/mm$^3$ or <350 cells/mm$^3$ with WHO stage or these chronic conditions.

Conclusion: In children with slow-progressing HIV, there is a substantial burden of chronic morbidity even when CD4 count is relatively preserved. Timely HIV testing and prompt ART initiation are urgently needed to prevent development of chronic complications.

Abstract Full-text [free] access

Editor’s notes: Substantial numbers of infants who have perinatally acquired HIV are presenting with HIV infection in later childhood or adolescence. It is estimated that a third of infants living with HIV are ‘slow-progressors’ with a median survival of 16 years. This study found a large burden of chronic morbidity among older children and adolescent at the time of HIV diagnosis. Interestingly, no association between CD4 count and WHO HIV disease stage was seen. Children with slow-progressing disease still appear go on to develop poor growth and chronic lung and skin disease despite preserved CD4 counts. Up until recently many of these children would not have been eligible to start ART based on the WHO 2013 HIV treatment guidelines. Recent changes to WHO guidelines recommending immediate ART for all, including older children, will hopefully reduce the risk of development of chronic complications in this population. Improved outcomes will only occur with timely diagnosis which requires increasing awareness of the burden of undiagnosed HIV disease, strengthening provider-initiated HIV testing and counselling and improving retention in ART care in this vulnerable age group.

Initiating antiretroviral therapy for HIV at a patient's first clinic visit: the RapIT randomized controlled trial.


Background: High rates of patient attrition from care between HIV testing and antiretroviral therapy (ART) initiation have been documented in sub-Saharan Africa, contributing to persistently low CD4 cell counts at treatment initiation. One reason for this is that starting ART in many countries is a lengthy and burdensome process, imposing long waits and multiple clinic visits on patients. We estimated the effect on uptake of ART and viral suppression of an accelerated initiation algorithm that allowed treatment-eligible patients to be dispensed their first supply of antiretroviral medications on the day of their first HIV-related clinic visit.
Methods and findings: RapIT (Rapid Initiation of Treatment) was an unblinded randomized controlled trial of single-visit ART initiation in two public sector clinics in South Africa, a primary health clinic (PHC) and a hospital-based HIV clinic. Adult (≥18 y old), non-pregnant patients receiving a positive HIV test or first treatment-eligible CD4 count were randomized to standard or rapid initiation. Patients in the rapid-initiation arm of the study ("rapid arm") received a point-of-care (POC) CD4 count if needed; those who were ART-eligible received a POC tuberculosis (TB) test if symptomatic, POC blood tests, physical exam, education, counseling, and antiretroviral (ARV) dispensing. Patients in the standard-initiation arm of the study ("standard arm") followed standard clinic procedures (three to five additional clinic visits over 2-4 wk prior to ARV dispensing). Follow up was by record review only. The primary outcome was viral suppression, defined as initiated, retained in care, and suppressed (≤400 copies/ml) within 10 mo of study enrollment. Secondary outcomes included initiation of ART ≤90 d of study enrollment, retention in care, time to ART initiation, patient-level predictors of primary outcomes, prevalence of TB symptoms, and the feasibility and acceptability of the intervention. A survival analysis was conducted comparing attrition from care after ART initiation between the groups among those who initiated within 90 d. Three hundred and seventy-seven patients were enrolled in the study between May 8, 2013 and August 29, 2014 (median CD4 count 210 cells/mm³). In the rapid arm, 119/187 patients (64%) initiated treatment and were virally suppressed at 10 mo, compared to 96/190 (51%) in the standard arm (relative risk [RR] 1.26 [1.05-1.50]). In the rapid arm 182/187 (97%) initiated ART ≤90 d, compared to 136/190 (72%) in the standard arm (RR 1.36, 95% confidence interval [CI], 1.24-1.49). Among 318 patients who did initiate ART within 90 d, the hazard of attrition within the first 10 mo did not differ between the treatment arms (hazard ratio [HR] 1.06; 95% CI 0.61-1.84). The study was limited by the small number of sites and small sample size, and the generalizability of the results to other settings and to non-research conditions is uncertain.

Conclusions: Offering single-visit ART initiation to adult patients in South Africa increased uptake of ART by 36% and viral suppression by 26%. This intervention should be considered for adoption in the public sector in Africa.

Abstract Full-text [free] access

Editor’s notes: This randomised controlled trial provides evidence that initiating ART at a single clinic visit limits pre-ART losses and increases the proportion in care with viral suppression within the first year of ART. Almost all people in the rapid arm initiated ART within 90 days. Attrition post-ART initiation remained quite high. One in three participants initiating ART in the rapid arm did not achieve the primary outcome of retention in care with viral suppression. However, this was not enough to offset the clear benefit of reduced pre-ART loss to follow-up.

There are a few things to note about the study. Firstly, the study design allowed for people who were enrolled at various stages in the pre-ART period, from HIV testing to receipt of CD4+ cell count. Fewer than half were enrolled on the day of HIV diagnosis. Secondly, the trial procedures relating to ART initiation were performed by research staff embedded in the health facilities. The one-stop ART initiation strategy was quite intensive, involving point-of-care testing for CD4+ cell count, TB, and routine pre-ART blood tests. This took over two hours for a single person, and more than four hours if TB testing was required. Lastly, the virologic suppression outcome was based on viral load measurement at any point between three and 12 months. It will therefore be particularly interesting to see longer-term data on virologic suppression and retention to see whether the effects were sustained.
The effectiveness and cost-effectiveness of this strategy should now be evaluated. The removal of CD4+ cell count eligibility criteria for ART might help to streamline the pre-initiation procedures, but additional effort might be required to make this process more efficient and suitable for implementation in routine care settings.

Antiretroviral therapy to prevent HIV acquisition in serodiscordant couples in a hyperendemic community in rural South Africa.


Background: Antiretroviral therapy (ART) was highly efficacious in preventing HIV transmission in stable serodiscordant couples in the HPTN-052 study, a resource-rich randomized controlled trial. However, minimal evidence exists of the effectiveness of ART in preventing HIV acquisition in stable serodiscordant couples in real-life population-based settings in hyperendemic communities of sub-Saharan Africa, where health systems are typically resource-poor and overburdened, adherence to ART is suboptimal, and HIV status disclosure to sexual partners is inconsistent.

Methods: Data arose from a population-based open cohort in KwaZulu-Natal, South Africa. HIV-uninfected individuals present between January 2005 and December 2013 (n=17 016) were included. Interval-censored time-updated proportional hazards regression was used to assess how the ART status affected HIV transmission risk in stable serodiscordant relationships.

Results: Of 17 016 individuals, 1846 had an HIV-uninfected and 196 had an HIV-infected stable partner over the follow-up period. HIV incidence was 3.8 per 100 person-years (100PY) among individuals with an HIV-infected partner (95% confidence interval [CI] 2.3-5.6), corresponding to 1.4 per 100PY (95% CI 0.4-3.5) among those with HIV-infected partners on ART and 5.6 per 100PY (95% CI 3.5-8.4) among those with partners not on ART. Use of ART was associated with a 77% decrease in HIV acquisition risk amongst serodiscordant couples (aHR=0.23, 95% CI 0.07-0.80).

Conclusions: ART initiation was associated with a very large reduction in HIV acquisition in serodiscordant couples in rural KwaZulu-Natal. However, real-life effectiveness was substantially lower than in the HPTN-052 trial. To eliminate HIV transmission in serodiscordant couples, additional prevention interventions are likely needed.

Abstract access

Editor’s notes: The landmark HPTN-052 multi-country trial among stable serodiscordant couples demonstrated that antiretroviral therapy (ART) substantially lowers the probability of transmission from HIV-positive people to their HIV-negative partners. However, the magnitude of effect of ART on transmission may not be generalisable to population level because in real-life settings, partnerships may not be stable, and there are operational challenges to programmatic delivery of ART at scale.

This study estimated the transmission risk in stable, serodiscordant couples, in a real-life setting in rural KwaZulu-Natal. The study included all stable serodiscordant couples in the community, whereas HPTN-052 enrolled individuals who presented to health services, and restricted recruitment to HIV-positive participants who disclosed their positive status to their partner.

The authors found that ART was associated with a decrease of 77% in transmission risk in this real-world setting, compared to a decrease of about 89% among people who immediately initiated ART in the HPTN-052 study.
The authors attributed this reduced effect size to a higher number of missed visits and lower adherence to ART in a real-life setting compared to the controlled trial. They also found fewer HIV-positive people with virologic suppression (77%, versus about 90% in the HPTN-052 trial) and lower disclosure rates (disclosure of HIV status to their partner was a requirement for inclusion in the trial).

The authors conclude that ART is highly effective in preventing HIV transmission in stable serodiscordant couples, but that to eliminate HIV transmission, additional preventive measures are necessary.

Relationship dynamics and partner beliefs about viral suppression: a longitudinal study of male couples living with HIV/AIDS (the duo project).


Accurate beliefs about partners’ viral suppression are important for HIV prevention and care. We fit multilevel mixed effects logistic regression models to examine associations between partners’ viral suppression beliefs and objective HIV RNA viral load tests, and whether relationship dynamics were associated with accurate viral suppression beliefs over time. Male couples (N = 266 couples) with at least one HIV-positive partner on antiretroviral therapy completed five assessments over 2 years. Half of the 407 HIV-positive partners were virally suppressed. Of the 40% who had inaccurate viral load beliefs, 80% assumed their partner was suppressed. The odds of having accurate viral load beliefs decreased over time (OR = 0.83; p = 0.042). Within-couple differences in dyadic adjustment (OR = 0.66; p < 0.01) and commitment (OR = 0.82; p = 0.022) were negatively associated with accurate viral load beliefs. Beliefs about a partner’s viral load may factor into sexual decision-making and social support. Couple-based approaches are warranted to improve knowledge of partners’ viral load.

Abstract access

Editor’s notes: This study with male couples in San Francisco examined how accurate a partner’s knowledge about their partner’s viral load status was, and if this changes over time. The study was the first of its kind. The research team enrolled 266 male couples where at least one of the couple was HIV-positive and on ART for >30 days. Most couples (72%) were seroconcordant (both HIV-positive) and 28% were serodiscordant. Participants were mostly white, middle-aged men with low-income levels. Eighty percent were living with their partner. The couples had been together on average 6.6 years. Thus, this sample may differ substantially from other studies with gay men and other men who have sex with men. Approximately 50% of men living with HIV on ART were virally suppressed at each of three visits. However, between 24% (visit one) and 40% (visit three) of men had inaccurate knowledge about their partner’s viral suppression, with most of these people wrongly believing their partner’s viral load to be suppressed when it was not. Surprisingly, these results were similar among serodiscordant and seroconcordant couples. Results did not differ significantly according to most relationship characteristics (relationship satisfaction; commitment; intimacy; equality; constructive communication).

The results are interesting because inaccuracy in partner’s beliefs about viral load suppression may translate into poor decision making around the safety of condomless anal intercourse. In addition, having accurate knowledge of partner viral suppression is important for the provision of social support associate with HIV care and treatment. Qualitative studies are necessary to understand why many men in this study had an inaccurate knowledge about their partner’s viral suppression. And why this inaccuracy increased over time. Understanding these issues and how they translate to other...
populations will be useful for developing programmes among male couples to reduce HIV transmission and increase partner’s social support associated with HIV care and treatment.

Estimating the impact of universal antiretroviral therapy for HIV serodiscordant couples through home HIV testing: insights from mathematical models.


Introduction: Antiretroviral therapy (ART) prevents HIV transmission within HIV serodiscordant couples (SDCs), but slow implementation and low uptake has limited its impact on population-level HIV incidence. Home HIV testing and counseling (HTC) campaigns could increase ART uptake among SDCs by incorporating couples' testing and ART referral. We estimated the reduction in adult HIV incidence achieved by incorporating universal ART for SDCs into home HTC campaigns in KwaZulu-Natal (KZN), South Africa, and southwestern (SW) Uganda.

Methods: We constructed dynamic, stochastic, agent-based network models for each region. We compared adult HIV incidence after 10 years under three scenarios: (1) "Current Practice," (2) "Home HTC" with linkage to ART for eligible persons (CD4 <350) and (3) "ART for SDCs" regardless of CD4, delivered alongside home HTC.

Results: ART for SDCs reduced HIV incidence by 38% versus Home HTC: from 1.12 (95% CI: 0.98-1.26) to 0.68 (0.54-0.82) cases per 100 person-years (py) in KZN, and from 0.56 (0.50-0.62) to 0.35 (0.30-0.39) cases per 100 py in SW Uganda. A quarter of incident HIV infections were averted over 10 years, and the proportion of virally suppressed HIV-positive persons increased approximately 15%.

Conclusions: Using home HTC to identify SDCs and deliver universal ART could avert substantially more new HIV infections than home HTC alone, with a smaller number needed to treat to prevent new HIV infections. Scale-up of home HTC will not diminish the effectiveness of targeting SDCs for treatment. Increasing rates of couples' testing, disclosure, and linkage to care is an efficient way to increase the impact of home HTC interventions on HIV incidence.

Abstract Full-text [free] access

Editor's notes: Delivering effective and efficient HIV prevention programmes to serodiscordant couples continues to be a challenge. The study used a dynamic stochastic agent–based network model to estimate the impact of universal antiretroviral therapy for serodiscordant couples. The authors examined the scaling up of antiretroviral therapy through home HIV testing and counselling in KwaZulu-Natal in South Africa and South-western Uganda. Data from South Africa and Uganda were used to compare three HIV programme scenarios. These included routine antiretroviral therapy delivery in the general population, routine antiretroviral therapy delivery in the general population and home HIV testing and counselling campaigns, and home HIV testing and counselling and delivery of antiretroviral therapy to serodiscordant couples during home HIV testing and counselling campaigns. The authors found that a combination of HIV prevention programmes that provide universal antiretroviral therapy for serodiscordant couples in the context of home HIV testing and counselling had more impact in reducing HIV incidence. The study demonstrated that home HIV testing and counselling and linkage to care HIV programmes can substantially reduce HIV incidence in South Africa and Uganda. This is a very interesting and well-designed modelling study which incorporates the effects of partnership dynamics in estimating the population level impact of HIV programmes.
2. Elimination of childhood infections


Background: Antiretroviral therapy (ART) and retention in care are essential for the prevention of mother-to-child HIV transmission (PMTCT). We aimed to assess the effect of a family-focused, integrated PMTCT care package.

Methods: In this parallel, cluster-randomised controlled trial, we pair-matched 12 primary and secondary level health-care facilities located in rural north-central Nigeria. Clinic pairs were randomly assigned to intervention or standard of care (control) by computer-generated sequence. HIV-infected women (and their infants) presenting for antenatal care or delivery were included if they had unknown HIV status at presentation (there was no age limit for the study, but the youngest participant was 16 years old); history of antiretroviral prophylaxis or treatment, but not receiving these at presentation; or known HIV status but had never received treatment. Standard of care included health information, opt-out HIV testing, infant feeding counselling, referral for CD4 cell counts and treatment, home-based services, antiretroviral prophylaxis, and early infant diagnosis. The intervention package added task shifting, point-of-care CD4 testing, integrated mother and infant service provision, and male partner and community engagement. The primary outcomes were the proportion of eligible women who initiated ART and the proportion of women and their infants retained in care at 6 weeks and 12 weeks post partum (assessed by generalised linear mixed effects model with random effects for matched clinic pairs). The trial is registered with ClinicalTrials.gov, number NCT01805752.

Findings: Between April 1, 2013, and March 31, 2014, we enrolled 369 eligible women (172 intervention, 197 control), similar across groups for marital status, duration of HIV diagnosis, and distance to facility. Median CD4 count was 424 cells per µL (IQR 268-606) in the intervention group and 314 cells per µL (245-406) in the control group (p<0.0001). Of the 369 women included in the study, 363 (98%) had WHO clinical stage 1 disease, 364 (99%) had high functional status, and 353 (96%) delivered vaginally. Mothers in the intervention group were more likely to initiate ART (166 [97%] vs 77 [39%]; adjusted relative risk 3.3, 95% CI 1.4-7.8). Mother and infant pairs in the intervention group were more likely to be retained in care at 6 weeks (125 [83%] of 150 vs 15 [9%] of 170; adjusted relative risk 9.1, 5.2-15.9) and 12 weeks (112 [75%] of 150 vs 11 [7%] of 168 pairs; 10.3, 5.4-19.7) post partum.

Interpretation: This integrated, family-focused PMTCT service package improved maternal ART initiation and mother and infant retention in care. An effective approach to improve the quality of PMTCT service delivery will positively affect global goals for the elimination of mother-to-child HIV transmission.

Abstract access

Editor’s notes: Nigeria currently has the highest prevalence of mother-to-child HIV transmission in the world. This is predominantly due to the limited coverage and delivery of effective prevention of mother-to-child HIV transmission programmes. Reported barriers to the scale up of effective
prevention programmes include a shortage of skilled health care workers, fragmented maternal and child health services and an absence of male participation in antenatal care. This parallel, cluster-randomised controlled study aimed to address these barriers. It explored the potential benefit of providing an innovative combination of prevention of mother-to-child HIV transmission programmes to pregnant women living with HIV in rural north-central Nigeria.

Standard care comprised of health information, opt-out HIV testing, infant feeding counselling, referral for CD4 cell counts and treatment, home-based services, antiretroviral prophylaxis, and early infant diagnosis. The design of the programme package took a family-focused approach. It also included integrated mother and infant service provision, male partner and community engagement, task shifting and point-of-care CD4 testing. The impact of this approach was positive. Women who were in the programme were more likely to initiate antiretroviral therapy and be retained in care at six weeks and twelve weeks post-partum. Of particular significance was a 74% reduction in incident HIV infection in infants born to women who were in the programme.

This study demonstrates an effective package but it is difficult to identify which specific components were the most beneficial. Nevertheless, the findings highlight Nigeria’s need to develop holistic packages of care if it is to achieve elimination of mother-to-child HIV transmission goals.

3. Key populations

Implementation and operational research: cohort analysis of program data to estimate HIV incidence and uptake of HIV-related services among female sex workers in Zimbabwe, 2009-2014.


Background: HIV epidemiology and intervention uptake among female sex workers (FSW) in sub-Saharan Africa remain poorly understood. Data from outreach programs are a neglected resource.

Methods: Analysis of data from FSW consultations with Zimbabwe’s National Sex Work program, 2009-2014. At each visit, data were collected on sociodemographic characteristics, HIV testing history, HIV tests conducted by the program and antiretroviral (ARV) history. Characteristics at first visit and longitudinal data on program engagement, repeat HIV testing, and HIV seroconversion were analyzed using a cohort approach.

Results: Data were available for 13 360 women, 31 389 visits, 14 579 reported HIV tests, 2750 tests undertaken by the program, and 2387 reported ARV treatment initiations. At first visit, 72% of FSW had tested for HIV; 50% of these reported being HIV positive. Among HIV-positive women, 41% reported being on ARV. 56% of FSW attended the program only once. FSW who had not previously had an HIV-positive test had been tested within the last 6 months 27% of the time during follow-up. After testing HIV positive, women started on ARV at a rate of 23/100 person years of follow-up. Among those with 2 or more HIV tests, the HIV seroconversion rate was 9.8/100 person years of follow-up (95% confidence interval: 7.1 to 15.9).

Conclusions: Individual-level outreach program data can be used to estimate HIV incidence and intervention uptake among FSW in Zimbabwe. Current data suggest very high HIV prevalence
and incidence among this group and help identify areas for program improvement. Further methodological validation is required.

**Abstract access**

**Editor’s notes:** Female sex workers in resource poor regions have been shown to have higher levels of HIV incidence and prevalence than people in the general population. Due to the highly stigmatised and often illegal nature of their work, these individuals are often marginalised in society. This can lead to poor engagement with the HIV testing and treatment programmes provided for the general population. Targeted outreach programmes for female sex workers such as the “Sisters for Change” programme in Zimbabwe described in this paper, aim to improve the engagement with testing and care for this group.

Collecting reliable data from female sex workers using a convenience sampling approach in order to estimate the prevalence of HIV is challenging due to the difficulty in ensuring the survey sample is representative of the wider female sex worker population. An alternative approach is respondent driven sampling (RDS) in which respondents recruit their peers to produce a generally representative sample of hard-to-reach populations. The results from RDS are however complex to analyse and interpret.

This paper presents an alternative approach using routinely collected data. Using the dates of programme visits, HIV tests (conducted both within and outside of the programme) and dates of antiretroviral initiation, the researchers generated estimates of HIV prevalence (number of positive tests/total number of tests) and HIV incidence (time at risk calculated from the first visit to an imputed date of seroconversion). They also identified risk factors associated with socio-demographic parameters or HIV testing history that were associated with a failure to continue engagement with the programme after a first visit. The prevalence and incidence results are consistent with results from a series of RDS surveys previously conducted in Zimbabwe by this research team.

A difficulty highlighted by the authors is that while this method improves on convenience sampling, it is still difficult to know how HIV incidence and prevalence among programme participants compares to that in the wider female sex worker population.

In summary this paper presents an approach by which similar programmes elsewhere could make better use of routinely collected data in order to generate estimates of impact and also identify subgroups of female sex workers with poorer engagement with care. This in turn could lead to a more effective targeting of limited resources.

**Effectiveness and safety of oral HIV pre-exposure prophylaxis (PrEP) for all populations: A systematic review and meta-analysis.**


Objective: Pre-exposure prophylaxis (PrEP) offers a promising new approach to HIV prevention. This systematic review and meta-analysis evaluated the evidence for use of oral PrEP containing tenofovir disoproxil fumarate (TDF) as an additional HIV prevention strategy in populations at substantial risk for HIV based on HIV acquisition, adverse events, drug resistance, sexual behavior, and reproductive health outcomes.

Design: Rigorous systematic review and meta-analysis.
Methods: A comprehensive search strategy reviewed three electronic databases and conference abstracts through April 2015. Pooled effect estimates were calculated using random-effects meta-analysis.

Results: Eighteen studies were included, comprising data from 39 articles and six conference abstracts. Across populations and PrEP regimens, PrEP significantly reduced the risk of HIV acquisition compared to placebo. Trials with PrEP use >70% demonstrated the highest PrEP effectiveness (RR = 0.30, 95% CI: 0.21-0.45, p < 0.001) compared to placebo. Trials with low PrEP use did not show a significantly protective effect. Adverse events were similar between PrEP and placebo groups. More cases of drug-resistant HIV infection were found among PrEP users who initiated PrEP while acutely HIV-infected, but incidence of acquiring drug-resistant HIV during PrEP use was low. Studies consistently found no association between PrEP use and changes in sexual risk behavior. PrEP was not associated with increased pregnancy-related adverse events or hormonal contraception effectiveness.

Conclusion: PrEP is protective against HIV infection across populations, presents few significant safety risks, and no evidence of behavioral risk compensation. The effective and cost-effective use of PrEP will require development of best practices for fostering uptake and adherence among people at substantial HIV-risk.

Abstract access

Editor’s notes: This systematic review is the first to aggregate data from across oral pre-exposure prophylaxis (PrEP) studies, including randomized control trials and observational studies, to present clear evidence on the effectiveness of oral PrEP use. The findings confirm that oral PrEP significantly reduces the risk of acquiring HIV if taken consistently and correctly across populations, countries, and most age groups. Differences in efficacy directly correlate with adherence, which accounts for the lower efficacy seen in some subgroups. Perhaps two of the most compelling analyses presented in this paper relate to resistance and behavioural disinhibition. The risk of resistance was shown to be quite low, and study participants exhibiting resistant HIV either enrolled in the studies during an acute infection stage or acquired resistant strains during the course of the research. Regarding behavioural disinhibition, indicators measured such as rates of sexually transmitted infections revealed that PrEP use in the efficacy trials was not associated with behavioural disinhibition and in some studies, resulted in even safer sexual behaviour than what was reported at baseline. Recently completed demonstration projects have reported increased rates of STIs among gay men and other men who have sex with men. However, in the open-label extensions included in this review, where counselling was more intensive, safer sex practices were maintained, thus suggesting that counselling can be effective in preventing behavioural disinhibition.

Integrated respondent-driven sampling and peer support for persons who inject drugs in Haiphong, Vietnam: a case study with implications for interventions.


Combined prevention for HIV among persons who inject drugs (PWID) has led to greatly reduced HIV transmission among PWID in many high-income settings, but these successes have not yet been replicated in resource-limited settings. Haiphong, Vietnam experienced a large HIV epidemic among PWID, with 68% prevalence in 2006. Haiphong has implemented needle/syringe programs, methadone maintenance treatment (MMT), and anti-retroviral treatment (ART), but there is an urgent need to identify high-risk PWID and link them to services. We examined integration of respondent-
driven sampling (RDS) and strong peer support groups as a mechanism for identifying high-risk PWID and linking them to services. The peer support staff performed the key tasks that required building and maintaining trust with the participants, including recruiting the RDS seeds, greeting and registering participants at the research site, taking electronic copies of participant fingerprints (to prevent multiple participation in the study), and conducting urinalyses. A 6-month cohort study with 250 participants followed the RDS cross-sectional study. The peer support staff maintained contact with these participants, tracking them if they missed appointments, and providing assistance in accessing methadone and ART. The RDS recruitment was quite rapid, with 603 participants recruited in three weeks. **HIV prevalence was 25%, Hepatitis C (HCV) prevalence 67%, and participants reported an average of 2.7 heroin injections per day.** Retention in the cohort study was high, with 86% of participants re-interviewed at 6-month follow-up. **Assistance in accessing services led to half of the participants in need of methadone enrolled in methadone clinics, and half of HIV-positive participants in need of ART enrolled in HIV clinics by the 6-month follow-up.** This study suggests that integrating large-scale RDS and strong peer support may provide a method for rapidly linking high-risk PWID to combined prevention and care, and greatly reducing HIV transmission among PWID in resource-limited settings.

Abstract access

**Editor’s notes:** This paper highlights that evidence on the effectiveness of harm reduction programmes including opioid substitution therapy, needle-syringe programmes and antiretroviral therapy, alone, and in combination have been shown to be effective in reducing incidence of HIV and hepatitis C in Europe, northern America and Australia. But evidence is lacking in countries with the largest or growing populations of people who inject drugs and high prevalence of HIV and hepatitis C. This is particularly true in low-income settings including South-East Asia and East Africa. But this is also true in high income countries such as the Russian Federation which has the fastest growing epidemic of HIV in the world, primarily among people who inject drugs. But opioid substitution therapy is prohibited. The paper is methodologically interesting. It demonstrates the feasibility of following-up a cohort of people who inject drugs over six months. More importantly, it illustrates how research can be used to link the most vulnerable members of the population, including people who inject frequently and people living with HIV who are not on treatment, into opioid substitution therapy and HIV treatment services. As well as demonstrating the practical use of research in increasing access to services, the research is also important for advocacy purposes. The authors illustrate the burden of HIV and hepatitis C among the population, further highlighting the need for harm reduction services and HIV/hepatitis C treatment.

**Exploring the relationship between population mobility and HIV risk: evidence from Tanzania.**


**Migration and population mobility has long been regarded as an important structural driver of HIV.** Following initial concerns regarding the spatial spread of the disease, mobile populations are viewed to engage in higher levels of risky sexual behaviours than non-mobile groups. However, beyond the case studies of mineworkers and truck drivers, the statistical evidence is inconclusive, suggesting that the relationship between mobility and risk is not well understood. This study investigated how engaging in specific livelihoods that involve mobility influences sexual behaviour and HIV risk. A qualitative research project, including focus groups and in-depth interviews with key mobile groups, was conducted in Northern Tanzania. **The findings show that the**
patterns and conditions of moving related to the requirements of each different economic activity influence the nature of relationships that mobile groups have whilst away, how and where local sexual networks are accessed, and the practicalities of having sex. This has further implications for condom use. Risk behaviours are also shaped by local sexual norms related to transactional sex, emphasising that the roles of mobility and gender are interrelated, overlapping and difficult to disentangle.

Abstract access

Editor’s notes: Case studies with truck drivers and mineworkers have clearly shown a relationship between migration, mobility and HIV risk in sub-Saharan Africa. It remains unclear to what extent findings from these case studies can be extrapolated across all mobile populations. Evidence from studies in other populations is inconclusive, inconsistent and in some cases contradictory. This, in part is due to the limitations of the statistical frameworks used which tend to reduce migration to an abstract individual variable and fail to recognise migration as a dynamic socio-economic phenomenon. These frameworks may also inadequately reflect the variability of migratory behaviour offering limited policy conclusions for addressing HIV risk arising from migration or population mobility.

This qualitative study was conducted in North-western Tanzania in a population in which 60% of men and 43% of women were classified as mobile. Data were collected through focus group discussions and individual interviews with both female and male farmers and maize traders.

The findings of this study suggest that patterns and conditions of moving can influence the nature of sexual relationships that mobile individuals have while away. The findings offer important insights for future, more nuanced statistical work. This would include considering why people move, where they go, patterns of movement, the specific economic activities in which they engage, and where they stay while they are away. The findings also highlight the importance of situating the risk behaviours of mobile individuals within the sexual norms and practices around sex and exchange, and particularly transactional sex. The authors note that being mobile may exacerbate gendered and economic inequalities making the relative influences of mobility and sexual norms difficult to disentangle. This further highlights the value of HIV prevention programmes being specifically tailored to the specific needs of mobile populations.

4. Elimination of gender inequalities

Effects of PREPARE, a multi-component, school-based HIV and intimate partner violence (IPV) prevention programme on adolescent sexual risk behaviour and IPV: cluster randomised controlled trial.


Young South Africans, especially women, are at high risk of HIV. We evaluated the effects of PREPARE, a multi-component, school-based HIV prevention intervention to delay sexual debut, increase condom use and decrease intimate partner violence (IPV) among young adolescents. We conducted a cluster RCT among Grade eights in 42 high schools. The intervention comprised education sessions, a school health service and a school sexual violence prevention programme. Participants completed questionnaires at baseline, 6 and 12 months.
Regression was undertaken to provide ORs or coefficients adjusted for clustering. Of 6244 sampled adolescents, 55.3% participated. At 12 months there were no differences between intervention and control arms in sexual risk behaviours. Participants in the intervention arm were less likely to report IPV victimisation (35.1 vs. 40.9%; OR 0.77, 95% CI 0.61-0.99; t(40) = 2.14) suggesting the intervention shaped intimate partnerships into safer ones, potentially lowering the risk for HIV.

Abstract access

Editor’s notes: Worldwide, HIV is one of the leading causes of death among adolescents. A key objective of the Global Strategy for Women’s, Children’s and Adolescents’ Health, launched in 2015, is to end the HIV epidemic by 2030. In South Africa, the prevalence and incidence of HIV remains high among young South Africans, especially among women. Early sexual debut and condomless sex are risk factors for HIV and other sexually transmitted infections. Another important risk factor in South Africa is the high level of intimate partner violence, which can also increase the risk of HIV infection among women. This cluster randomised trial sought to address these risk factors among young adolescents (average age 13 years) in public high schools in the Western Cape. The education component of the programme comprised 21 sessions delivered weekly immediately after school. One explanation for the lack of an effect on sexual behaviour was sub-optimal exposure to the activity as a result of poor attendance at sessions. Overall, the mean attendance was 8.02 sessions with higher attendance among girls than among boys. Even so, self-reported intimate partner violence – a factor that predisposes HIV infection – was reduced. The investigators suggest that this may be because attendance was higher at earlier sessions, which addressed gender issues, so more participants received exposure to content associated with intimate partner violence than sexual behaviour.

Achieving high, sustained attendance rates at after-school programmes is challenging and as the investigators note, perhaps the most efficient way to ensure that adolescents receive adequate exposure to HIV risk reduction programmes is to embed them in the school curriculum. However, programmes also need to address other structural, social and environmental factors affecting HIV infection.


Background: Intimate partner violence (IPV) is associated with higher HIV incidence, reduced condom use, and poor adherence to antiretroviral therapy and other medications. IPV may also affect adherence to pre-exposure prophylaxis (PrEP).

Methods: We analyzed data from 1785 HIV-uninfected women enrolled in a clinical trial of PrEP among African HIV-serodiscordant couples. Experience of verbal, physical, or economic IPV was assessed at monthly visits by face-to-face interviews. Low PrEP adherence was defined as clinic-based pill count coverage <80% or plasma tenofovir levels <40 ng/mL. The association between IPV and low adherence was analyzed using generalized estimating equations, adjusting for potential confounders. In-depth interview transcripts were examined to explain how IPV could impact adherence.
Results: 16% of women reported IPV during a median of 34.8 months of follow-up (IQR 27.0 - 35.0). Overall, 7% of visits had pill count coverage <80% and 32% had plasma tenofovir <40 ng/mL. Women reporting IPV in the past 3 months had increased risk of low adherence by pill count (adjusted RR 1.49, 95% CI 1.17-1.89) and by plasma tenofovir (adjusted RR 1.51, 95% CI 1.06-2.15). Verbal, economic, and physical IPV were all associated with low adherence. However, the impact of IPV diminished and was not statistically significant 3 months after the reported exposure. In qualitative interviews, women identified several ways in which IPV affected adherence, including stress and forgetting, leaving home without pills, and partners throwing pills away.

Conclusion: Women who reported recent IPV in the Partners PrEP Study were at increased risk of low PrEP adherence. Strategies to mitigate PrEP non-adherence in the context of IPV should be evaluated.

Editor’s notes: The high rates of HIV infection in women underscore persistent gender inequalities, in particular that of violence against women. Intimate partner violence (IPV) puts women at increased risk of HIV infection. Further, among women living with HIV, IPV has also been associated with lower rates of treatment uptake and adherence to antiretroviral therapy (ART). The interaction between IPV and HIV is complex, and includes biological, socio-economic and cultural mechanisms. This is the first study to examine the association between IPV and adherence to HIV pre-exposure prophylaxis (PrEP). Women who had experienced IPV in the past three months were 50% more likely than women who had never experienced IPV to have poor adherence, as measured by both pills counts and drug levels in the blood. Recent IPV was also associated with an increase in the risk of HIV infection. Women in the study were in stable, serodiscordant relationships, had enrolled in the study together with their partners, and were using PrEP with their partner’s consent. The proportion of women reporting IPV during the study was much lower than national estimates in the region. These findings are thus of concern for PrEP demonstration projects focusing on key populations at high risk of HIV, who may experience higher rates of IPV and be less likely to have partner support.

PrEP is a key element of combination HIV prevention strategies in high-risk populations, but requires high adherence in order to be effective. Programmes focusing on promoting PrEP adherence in women who have experienced violence are urgently needed. More broadly, HIV prevention programmes should be expanded to integrate IPV prevention as an important component to reducing women’s risk of HIV.

5. Financing

Effectiveness of and financial returns to voluntary medical male circumcision for HIV prevention in South Africa: an incremental cost-effectiveness analysis.


Background: Empirical studies and population-level policy simulations show the importance of voluntary medical male circumcision (VMMC) in generalized epidemics. This paper complements available scenario-based studies (projecting costs and outcomes over some policy period, typically spanning decades) by adopting an incremental approach-analyzing the expected consequences of circumcising one male individual with specific characteristics in a specific year. This approach yields more precise estimates of VMMC's cost-effectiveness and
identifies the outcomes of current investments in VMMC (e.g., within a fiscal budget period) rather than of investments spread over the entire policy period.

Methods/findings: The model has three components. We adapted the ASSA2008 model, a demographic and epidemiological model of the HIV epidemic in South Africa, to analyze the impact of one VMMC on HIV incidence over time and across the population. A costing module tracked the costs of VMMC and the resulting financial savings owing to reduced HIV incidence over time. Then, we used several financial indicators to assess the cost-effectiveness of and financial return on investments in VMMC. One circumcision of a young man up to age 20 prevents on average over 0.2 HIV infections, but this effect declines steeply with age, e.g., to 0.08 by age 30. Net financial savings from one VMMC at age 20 are estimated at US$617 at a discount rate of 5% and are lower for circumcisions both at younger ages (because the savings occur later and are discounted more) and at older ages (because male circumcision becomes less effective). Investments in male circumcision carry a financial rate of return of up to 14.5% (for circumcisions at age 20). The cost of a male circumcision is refinanced fastest, after 13 y, for circumcisions at ages 20 to 25. Principal limitations of the analysis arise from the long time (decades) over which the effects of VMMC unfold—the results are therefore sensitive to the discount rate applied, and more generally to the future course of the epidemic and of HIV/AIDS-related policies pursued by the government.

Conclusions: VMMC in South Africa is highly effective in reducing both HIV incidence and the financial costs of the HIV response. The return on investment is highest if males are circumcised between ages 20 and 25, but this return on investment declines steeply with age.

Abstract  Full-text [free] access

Editor's notes: Voluntary medical male circumcision is known to be an effective HIV-infection prevention method. While many models and papers have explored the cost and cost-effectiveness of voluntary medical male circumcision at a population level, the authors carry out their analysis using an incremental approach, looking at the expected consequences of circumcising one male individual within a specific year. Their findings are consistent with previous work on the topic, namely that voluntary medical male circumcision is highly effective in countries with high HIV prevalence and is, under many circumstances, cost-saving. They also find that voluntary medical male circumcision is most effective when performed at age 20, and effectiveness declines at higher ages due to diminished direct and indirect effects on HIV incidence.

While it would indeed be wise for countries to consider long-term impacts of programmes, governments often make decisions in the short-term. It is therefore important for governments to understand the benefits of a programme or policy that are accrued during the timeframe of presidential or congressional terms. The findings and the approach used in this study are very important because they present evidence of impact of investment within a government’s current budget process. By providing a way to measure the immediate return on investment, the authors of this paper help inform policymakers in a way that is tangible, pragmatic, and, unfortunately, not often used.

Health expenditure and catastrophic spending among older adults living with HIV.

Introduction: The burden of HIV is increasing among adults aged over 50, who generally experience increased risk of comorbid illnesses and poorer financial protection. We compared patterns of health utilisation and expenditure among HIV-positive and HIV-negative adults over 50.

Methods: Data were drawn from the Study on global AGEing and adult health in South Africa with analysis focusing on individual and household-level data of 147 HIV-positive and 2725 HIV-negative respondents.

Results: HIV-positive respondents reported lower utilisation of private health-care facilities (11.8%) than HIV-negative respondents (25.0%) (p = .03) and generally had more negative attitudes towards health system responsiveness than HIV-negative counterparts. Less than 10% of HIV-positive and HIV-negative respondents experienced catastrophic health expenditure (CHE). Women (OR 1.8; p < .001) and respondents from rural settings (OR 2.9; p < .01) had higher odds of CHE than men or respondents in urban settings. Over half the respondents in both groups indicated that they had received free health care.

Conclusions: These findings suggest that although HIV-positive and HIV-negative older adults in South Africa are protected to some extent from CHE, inequalities still exist in access to and quality of care available at health-care services - which can inform South Africa's development of a national health insurance scheme.

Abstract access

Editor’s notes: The study provides a valuable overview of the health expenditures of HIV-positive and negative older people (50 years and older) in South Africa. It should be noted that the data used in this analysis are from 2007-2008. Therefore, it is likely that some things may have changed as anti-retroviral therapy has become more available. Perhaps some of the negative experiences reported by people living with HIV may have changed. However, it is likely that waiting times in clinics and concerns about drug-stockouts, may not have changed. Nearly a decade on, the number of people in need of HIV-associated care, and the resulting burden on the health service remain immense. The authors point to the valuable role of the social security system in reducing the financial impact of HIV, and mitigating catastrophic health expenditures.

The authors have produced an important paper, highlighting some of the inequities in health care access. Many of these inequities are likely to have persisted. It would be invaluable to have a similar analysis of more recent data in order to chart progress.

Cost-effectiveness of injectable preexposure prophylaxis for HIV prevention in South Africa.


Background: Long-acting injectable antiretrovirals such as rilpivirine (RPV) could promote adherence to preexposure prophylaxis (PrEP) for HIV prevention. However, the cost-effectiveness of injectable PrEP is unclear.

Methods: We constructed a dynamic model of the heterosexual HIV epidemic in KwaZulu-Natal, South Africa, and analyzed scenarios of RPV PrEP scale-up for combination HIV prevention in comparison with a reference scenario without PrEP. We estimated new HIV infections, life-years and costs, and incremental cost-effectiveness ratios, over ten-year and lifetime horizons, assuming a societal perspective.
Results: **Compared with no PrEP, unprioritized scale-up of RVP PrEP covering 2.5%-15% of adults prevented up to 9% of new infections over ten years.** HIV prevention doubled (17%) when the same coverage was prioritized to 20-29 year-old women, costing $10 880-$19 213 per infection prevented. Prioritization of PrEP to 80% of individuals at highest behavioral risk achieved comparable prevention (4%-8%) at <1% overall coverage, costing $298-$1242 per infection prevented. Over lifetime, **PrEP scale-up among 20-29 year-old women was very cost-effective (<$1600 per life-year gained), dominating unprioritized PrEP** while risk-prioritization was cost-saving. PrEP’s ten-year impact decreased by almost 50% with increases in incremental cost-effectiveness ratios (up to 4.2-fold) in conservative base-case analysis. **Sensitivity analysis identified PrEP’s costs, efficacy and reliability of delivery, as the principal drivers of uncertainty in PrEP’s cost-effectiveness, and PrEP remained cost-effective under the assumption of universal access to second-line antiretroviral therapy.**

Conclusions: **Compared with no PrEP, prioritized scale-up of RPV PrEP in KwaZulu-Natal could be very cost-effective or cost-saving, but suboptimal PrEP would erode benefits and increase costs.**

Abstract access

**Editor’s notes:** Pre-exposure prophylaxis (PrEP) has been shown to work when people are able to use it well. But recent trials have illustrated that people are not always able to take tablets or use vaginal gels frequently enough to maximise protection. A promising area in HIV prevention research is long-lasting injectable PrEP, which would only require application once every month or so. This paper estimates whether injectable PrEP might be cost effective in South Africa. The authors explore how this form of PrEP should be targeted to different groups. Injectable PrEP is estimated to be very cost-effective in general, and would save money if people at highest risk were able to gain access. However, because an injectable product has not been fully developed yet, this analysis requires many assumptions. The authors test how changes in these assumptions might give a different conclusion. They find that the most important factors are the cost of injectable PrEP products themselves, how well they work, and whether they can be made available to people who need them.

6. Health systems and services

**Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in HIV-positive adults.**


Background: Rapid detection of tuberculosis (TB) among people living with human immunodeficiency virus (HIV) is a global health priority. HIV-associated TB may have different clinical presentations and is challenging to diagnose. **Conventional sputum tests have reduced sensitivity in HIV-positive individuals, who have higher rates of extrapulmonary TB compared with HIV-negative individuals.** The lateral flow urine lipoarabinomannan assay (LF-LAM) is a new, commercially available point-of-care test that detects lipoarabinomannan (LAM), a lipopolysaccharide present in mycobacterial cell walls, in people with active TB disease.

Objectives: **To assess the accuracy of LF-LAM for the diagnosis of active TB disease in HIV-positive adults who have signs and symptoms suggestive of TB (TB diagnosis). To assess the**
accuracy of LF-LAM as a screening test for active TB disease in HIV-positive adults irrespective of signs and symptoms suggestive of TB (TB screening).

Search methods: We searched the following databases without language restriction on 5 February 2015: the Cochrane Infectious Diseases Group Specialized Register; MEDLINE (PubMed, 1966); EMBASE (OVID, from 1980); Science Citation Index Expanded (SCI-EXPANDED, from 1900), Conference Proceedings Citation Index-Science (CPCI-S, from 1900), and BIOSIS Previews (from 1926) (all three using the Web of Science platform; MEDION; LILACS (BIREME, from 1982); SCOPUS (from 1995); the metaRegister of Controlled Trials (mRCT); the search portal of the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP); and ProQuest Dissertations & Theses A&I (from 1861).

Selection criteria: Eligible study types included randomized controlled trials, cross-sectional studies, and cohort studies that determined LF-LAM accuracy for TB against a microbiological reference standard (culture or nucleic acid amplification test from any body site). A higher quality reference standard was one in which two or more specimen types were evaluated for TB, and a lower quality reference standard was one in which only one specimen type was evaluated for TB. Participants were HIV-positive people aged 15 years and older.

Data collection and analysis: Two review authors independently extracted data from each included study using a standardized form. We appraised the quality of studies using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. We evaluated the test at two different cut-offs: (grade 1 or 2, based on the reference card scale of five intensity bands). Most analyses used grade 2, the manufacturer's currently recommended cut-off for positivity. We carried out meta-analyses to estimate pooled sensitivity and specificity using a bivariate random-effects model and estimated the models using a Bayesian approach. We determined accuracy of LF-LAM combined with sputum microscopy or Xpert(R) MTB/RIF. In addition, we explored the influence of CD4 count on the accuracy estimates. We assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results: We included 12 studies: six studies evaluated LF-LAM for TB diagnosis and six studies evaluated the test for TB screening. All studies were cross-sectional or cohort studies. Studies for TB diagnosis were largely conducted among inpatients (median CD4 range 71 to 210 cells per µL) and studies for TB screening were largely conducted among outpatients (median CD4 range 127 to 437 cells per µL). All studies were conducted in low- or middle-income countries. Only two studies for TB diagnosis (33%) and one study for TB screening (17%) used a higher quality reference standard LF-LAM for TB diagnosis (grade 2 cut-off); meta-analyses showed median pooled sensitivity and specificity (95% credible interval (CrI)) of 45% (29% to 63%) and 92% (80% to 97%), (five studies, 2313 participants, 35% with TB, low quality evidence). The pooled sensitivity of a combination of LF-LAM and sputum microscopy (either test positive) was 59% (47% to 70%), which represented a 19% (4% to 36%) increase over sputum microscopy alone, while the pooled specificity was 92% (73% to 97%), which represented a 6% (1% to 24%) decrease from sputum microscopy alone (four studies, 1876 participants, 38% with TB). The pooled sensitivity of a combination of LF-LAM and sputum Xpert(R) MTB/RIF (either test positive) was 75% (61% to 87%) and represented a 13% (1% to 37%) increase over Xpert(R) MTB/RIF alone. The pooled specificity was 93% (81% to 97%) and represented a 4% (1% to 16%) decrease from Xpert(R) MTB/RIF alone (three studies, 909 participants, 36% with TB). Pooled sensitivity and specificity of LF-LAM were 56% (41% to 70%) and 90% (81% to 95%) in participants with a CD4 count of less than or equal to 100 cells per µL (five studies, 859 participants, 47% with TB) versus 26% (16% to 46%) and 92% (78% to 97%) in participants with a CD4 count greater than 100 cells per µL (five studies, 1410
participants, 30% with TB). LF-LAM for TB screening (grade 2 cut-off): for individual studies, sensitivity estimates (95% CrI) were 44% (30% to 58%), 28% (16% to 42%), and 0% (0% to 71%) and corresponding specificity estimates were 95% (92% to 97%), 94% (90% to 97%), and 95% (92% to 97%) (three studies, 1055 participants, 11% with TB, very low quality evidence). There were limited data for additional analyses. The main limitations of the review were the use of a lower quality reference standard in most included studies, and the small number of studies and participants included in the analyses. The results should, therefore, be interpreted with caution.

Authors' conclusions: We found that LF-LAM has low sensitivity to detect TB in adults living with HIV whether the test is used for diagnosis or screening. For TB diagnosis, the combination of LF-LAM with sputum microscopy suggests an increase in sensitivity for TB compared to either test alone, but with a decrease in specificity. In HIV-positive individuals with low CD4 counts who are seriously ill, LF-LAM may help with the diagnosis of TB.

Abstract  Full-text [free] access

Editor's notes: Tuberculosis (TB) remains a leading cause of death among people living with HIV. Diagnostic tests for TB are suboptimal, and a test for TB with adequate performance which could be used by nurses in primary care clinics would be a great advance. Lipoarabinomannam (LAM) is a component of mycobacterial cell wall which can be found in urine. A lateral flow assay to detect LAM in urine is commercially available at low cost, and can be used in primary care settings without the need for laboratory equipment. However the test is insensitive, such that it has no useful role among HIV-negative people, but has better sensitivity among people living with HIV, leading to questions concerning its role in TB diagnostic pathways.

This systematic review puts together data concerning the performance of the LAM lateral flow assay when used either as a screening test or for diagnosis of TB among people living with HIV. Assessment is made more complicated because the recommended reference cut-off for the test has been changed, with relatively few studies performed after the recommended cut off became what is referred to here as the “higher quality” reference standard (grade two test band intensity, rather than grade one as was previously recommended). Based on the grade two cut–off, the pooled estimate of sensitivity of the test was 45%. As expected, sensitivity was better for individuals with low CD4 counts.

This review informed WHO recommendations on the use of the LAM assay, suggesting that its use should be restricted to assisting with TB diagnosis in people living with HIV with low CD4 counts who are seriously ill. This is consistent with the results of the recent trial (PMID: 26970721) comparing management of hospitalised HIV-positive people reporting one or more TB symptoms with routine testing of urine for LAM compared to standard diagnostic tests, which found that the addition of LAM testing resulted in a small reduction in eight-week mortality.

Overall, LAM is inadequate as a single test for TB, and an accurate diagnostic test that could be used in-session for TB diagnosis in primary care clinics remains a pressing priority.

Antiretroviral choice for HIV impacts antimalarial exposure and treatment outcomes in Ugandan children.

Background: The optimal treatment of malaria in HIV-infected children requires consideration of critical drug-drug interactions in co-infected children, as these may significantly impact drug exposure and clinical outcomes.

Methods: We conducted an intensive and sparse pharmacokinetic and pharmacodynamic study in Uganda of the most widely adopted artemisinin-based combination therapy, artemether-lumefantrine. HIV-infected children on three different first-line antiretroviral therapies (ART) were compared to HIV-uninfected children not on ART, all of whom required treatment for Plasmodium falciparum malaria. Pharmacokinetic sampling for artemether, dihydroartemisinin (DHA) and lumefantrine exposure was conducted through day 21, and associations between drug exposure and outcomes through day 42 were investigated.

Results: 145 and 225 children were included in the intensive and sparse pharmacokinetic analyses, respectively. Compared to no ART, efavirenz reduced exposure to all antimalarial components by 2.1 to 3.4-fold; lopinavir/ritonavir increased lumefantrine exposure by 2.1-fold; and nevirapine reduced artemether exposure only. Day 7 concentrations of lumefantrine were 10-fold lower in children on efavirenz versus lopinavir/ritonavir-based ART, changes that were associated with approximately 4-fold higher odds of recurrent malaria by day 28 in those on efavirenz versus lopinavir/ritonavir-based ART.

Conclusions: The choice of ART in children living in a malaria-endemic region has highly significant impacts on the pharmacokinetics and pharmacodynamics of artemether-lumefantrine treatment. Efavirenz-based ART reduces all antimalarial components and is associated with the highest risk of recurrent malaria following treatment. For those on efavirenz, close clinical follow-up for recurrent malaria following artemether-lumefantrine treatment, along with the study of modified dosing regimens that provide higher exposure is warranted.

Abstract access

Editor's notes: This study looks at the pharmacokinetic (PK) and clinical outcomes for artemether/lumefantrine therapy of falciparum malaria in Ugandan children aged 1-8 years living without and with HIV on antiretroviral therapy (ART) regimes containing efavirenz, nevirapine or lopinavir. The stand-out result is that malaria outcomes were better in children who were taking lopinavir-based ART, without any significant drug adverse effects.

The most commonly-used ART combinations have extensive interactions with other classes of drugs. The effects of these interactions on clinical outcomes cannot always be accurately predicted from PK studies in healthy adults. This is especially so for sick children whose drug handling may be different. Large PK studies of unwell children are difficult to do, so this study is a rare gem. In fact the PK results are largely as expected. Exposure to artemether and its active metabolite are reduced by efavirenz and nevirapine; and exposure to lumefantrine is reduced by efavirenz and increased by lopinavir with ritonavir. Lumefantrine is the component of the combination malaria therapy with a longer effect and is intended to provide protection from recurrence.

The big question is, what is the impact of these PK differences on clinical outcomes? This is where it gets complicated. In total some 370 malaria episodes were studied. The authors illustrate that the efavirenz group had substantially higher malaria recurrence than the lopinavir group. The lopinavir group had the highest levels of lumefantrine. The efavirenz group had similar outcomes to the HIV-negative group, despite having lower levels of lumefantrine.

The recurrence rate in this study, in an area of intense malaria transmission, is dominated by early reinfection rather than recrudesence. The great majority of children taking ART were also taking co-
trimoxazole, which provides protection against malaria infection, giving all children taking ART additional protection versus malaria compared to HIV-negative children. The difference between the efavirenz and lopinavir groups is likely to be due to lumefantrine levels. Higher levels of lumefantrine persist in combination with lopinavir/ritonavir – an effect that might also apply to other protease inhibitors. WHO guidelines recommend lopinavir/ritonavir as part of first-line ART for children under three years old. Whether this effect is large enough to influence ART choices in older children will depend on local circumstances, particularly the malaria transmission rate.