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

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UNAIDS
1. HIV testing and treatment

Incidence of opportunistic infections and the impact of antiretroviral therapy among HIV-infected adults in low and middle income countries: a systematic review and meta-analysis.


Background: To understand regional burdens and inform delivery of health services, we conducted a systematic review and meta-analysis to evaluate the effect of antiretroviral therapy (ART) on incidence of key opportunistic infections (OIs) in HIV-infected adults in low and middle-income countries (LMIC).

Methods: Eligible studies describing the cumulative incidence of OIs and proportion on ART from 1990 to November 2013 were identified using multiple databases. Summary incident risks for the ART-naive period, and during and after the first year of ART, were calculated using random effects meta-analyses. Summary estimates from ART subgroups were compared using meta-regression. The number of OI cases and associated costs averted if ART was initiated at CD4 ≥200 cells/µl was estimated using UNAIDS country estimates and global average OI treatment cost per case.

Results: We identified 7965 citations, and included 126 studies describing 491,608 HIV-infected persons. In ART-naive patients, summary risk was highest (>5%) for oral candidiasis, tuberculosis, herpes zoster, and bacterial pneumonia. The reduction in incidence was greatest for all OIs during the first 12 months of ART (range 57-91%) except for tuberculosis, and was largest for oral candidiasis, PCP and toxoplasmosis. Earlier ART was estimated to have averted 857,828 cases in 2013 (95% confidence interval [CI], 828,032-874,853), with cost savings of $46.7 million (95% CI, 43.8-49.4).

Conclusions: There was a major reduction in risk for most OIs with ART use in LMICs, with the greatest effect seen in the first year of treatment. ART has resulted in substantial cost savings from OIs averted.

Abstract Full-text [free] access

Editor’s notes: Opportunistic infections (OIs) remain the major cause of HIV-associated mortality. OIs account for substantially higher mortality in low and middle income countries (LMICs) compared to high income countries (HICs).

This paper describes the results of a systematic review and meta-analysis including about 500,000 people on ART in LMICs across three regions (sub-Saharan Africa, Asia, and Latin America). These large numbers enabled the investigators to look at the effect of ART on the incidence of key OIs during and after the first year of treatment.

Not surprisingly they found that the effect of ART reduced the risk of all OIs during the first year after ART initiation, although the reduction was less for tuberculosis. The authors attribute this to the occurrence of tuberculosis across a wide range of CD4 cell counts, a smaller effect of early immune restoration and the contribution of TB as a manifestation of immune reconstitution syndrome during the first months after ART initiation. Beyond one year after ART initiation, the reduction in tuberculosis was greater.

They conclude that the effect of ART on the incidence of most HIV-associated OIs is the key reason for the global decline in HIV-associated mortality. However, a significant proportion of HIV-positive
persons still continue to present with advanced disease. Besides timely ART initiation, additional measures such as CTX prophylaxis, screening for TB and cryptococcal disease, and the use of isoniazid and fluconazole prophylaxis should be considered for late presenters.


Background: Cryptococcus is the most common cause of adult meningitis in Africa. We assessed the safety and microbiological efficacy of adjunctive sertraline, previously shown to have in-vitro and in-vivo activity against cryptococcus.

Methods: In this open-label dose-finding study, we recruited HIV-infected individuals with cryptococcal meningitis who presented to Mulago Hospital in Kampala, Uganda between Aug 14, 2013, and Aug 30, 2014. To assess safety and tolerability, the first 60 participants were given sertraline at escalating doses of 100 mg/day, 200 mg/day, 300 mg/day, or 400 mg/day as induction therapy for 2 weeks, followed by consolidation therapy with 200 mg/day for an additional 8 weeks. From Nov 29, 2013, participants were randomly assigned (1:1) to receive open-label sertraline at predetermined doses of 200 mg/day, 300 mg/day, or 400 mg/day as induction therapy for 2 weeks, followed by consolidation therapy with 200 mg/day for 8 weeks. Dose assignment was made via computer-generated, permuted block randomisation stratified by antiretroviral therapy (ART) status for people with a first episode of meningitis. The primary outcome was 2-week cerebrospinal fluid (CSF) clearance rate of cryptococcus, termed early fungicidal activity, measured in patients with a first episode of culture-positive meningitis and two or more CSF cultures. This study is registered with ClinicalTrials.gov, number NCT01802385.

Findings: Of the 330 individuals assessed, 172 HIV-infected adults with cryptococcal meningitis were enrolled. We gave 100 mg/day sertraline to 17 patients, 200 mg/day to 12 patients, 300 mg/day to 14 patients, and 400 mg/day to 17 patients. 112 participants were randomly assigned to receive sertraline at 200 mg (n=48), 300 mg (n=36), or 400 mg (n=28) daily for the first 2 weeks, and 200 mg/day thereafter. The final population consisted of 17 participants in the 100 mg group, 60 in the 200 mg group, 50 in the 300 mg group, and 45 in the 400 mg in group. Participants receiving any sertraline dose averaged a CSF clearance rate of -0.37 colony forming units per mL per day (95% CI -0.41 to -0.33). Incidence of paradoxical immune reconstitution inflammatory syndrome was 5% (two of 43 newly starting ART) and no cases of relapse occurred over the 12-week study period. 38 (22%) of 172 participants had died at 2 weeks, and 69 (40%) had died at 12 weeks. Six grade 4 adverse events occurred in 17 participants receiving 100 mg, 14 events in 60 participants receiving 200 mg, 19 events in 50 participants receiving 300 mg, and eight events in 45 participants receiving 400 mg. Grade 4 or 5 adverse event risk did not differ between current US Food and Drug Administration-approved dosing of 100-200 mg/day and higher doses of 300-400 mg/day (hazard ratio 1.27, 95% CI 0.69-2.32; p=0.45).

Interpretation: Participants receiving sertraline had faster cryptococcal CSF clearance and a lower incidence of immune reconstitution inflammatory syndrome and relapse than that reported in the past. This inexpensive and off-patent oral medication is a promising adjunctive antifungal therapy.
Abstract  Full-text [free] access

Editor’s notes: Mortality from cryptococcal meningitis remains unacceptably high, especially in low-income settings. This is partly due to high cost and limited availability of effective antifungal agents. Even when antifungal drugs are available, toxic side effects and suboptimal clearance of cryptococcus from the cerebrospinal fluid (CSF) result in continued morbidity and mortality. There is an urgent need for new effective antifungal drugs in the treatment of cryptococcal meningitis which improve the rate of CSF sterilisation, have low toxicity, and are readily available.

Sertraline, a commonly used selective serotonin reuptake inhibitor antidepressant with excellent brain parenchymal penetration, has been shown to have potent in vitro and in vivo fungicidal activity against cryptococcus in mice. This is the first clinical study in humans to assess the efficacy of adjunctive sertraline for cryptococcal meningitis, when added to standard amphotericin B and high-dose fluconazole antifungal treatment. Faster cryptococcal CSF clearance and lower incidence of immune reconstitution inflammatory syndrome and relapse were seen in people receiving oral sertraline compared to a historical cohort. Repurposing of sertraline, a drug which is widely available, non-toxic and affordable, as an effective novel adjunctive fungicidal agent shows early promise. It is yet to be seen if improved cryptococcal CSF clearance will translate into better survival. We will have to wait until 2018 to see the outcome of the Adjunctive Sertraline for the Treatment of Cryptococcal Meningitis (ASTRO-CM) randomised clinical trial.

Incidence and prevalence of opportunistic and other infections and the impact of antiretroviral therapy among HIV-infected children in low and middle-income countries: a systematic review and meta-analysis.


Background: We conducted a systematic review and meta-analysis to evaluate the incidence and prevalence of 14 opportunistic infections (OIs) and other infections as well as the impact of antiretroviral therapy (ART) among HIV-infected children (<18 years) in low and middle-income countries (LMIC), to understand regional burden of disease, and inform delivery of HIV services.

Methods: Eligible studies described the incidence of OIs and other infections in ART-naive and exposed children from January 1990 to November 2013, using Medline, Global Health, Embase, Cinnah, Web of Knowledge and Lilacs databases. Summary incident risk and prevalent risk for each OI in ART-naive and ART-exposed children were calculated, and unadjusted odds ratios calculated for impact of ART. The number of OI cases and associated costs averted were estimated using the AIM model.

Results: We identified 4542 citations, and 88 studies were included, comprising 55 679 HIV-infected children. Bacterial pneumonia and tuberculosis were the most common incident and prevalent infections in both ART-naive and ART-exposed children. There was a significant reduction in incident risk with ART for the majority of OIs. There was a smaller impact on bacterial sepsis and pneumonia, and an increase observed for varicella zoster. ART initiation based on 2010 WHO guidelines criteria for ART initiation in children was estimated to potentially avert more than 161 000 OIs (2013 UNAIDS data) with estimated cost savings of at least USD $17 million per year.

Conclusion: There is a substantial decrease in the risk of most OIs with ART use in HIV-infected children in LMIC, and estimated large potential cost savings in OIs averted with ART use, although there are greater limitations in paediatric data compared to adults.
Abstract Full-text [free] access

Editor’s notes: The scale-up of programmes to prevent mother-to-child HIV transmission has resulted in a 60% decline in paediatric HIV infections. The scale-up of antiretroviral therapy (ART), however, has been less successful in children, with only a third of eligible children aged under 15 years receiving ART as of 2014. In high-income countries, there has been a substantial decrease in the incidence of most opportunistic infections (OIs) following the introduction of ART. The impact of ART on burden of OIs in low and middle income countries (LMICs) is much less well-understood.

This meta-analysis estimated the incidence and prevalence of 14 key OIs and other infections in children (aged 0-18 years) before and after the introduction of ART across three geographical regions, namely sub-Saharan Africa, Latin America and the Caribbean, and Asia.

The use of ART has resulted in a decline in incidence of all but three infections, namely tuberculosis, pneumonia and candidiasis. These remain the most common incident and prevalent infections in ART-naïve and ART-exposed children. It is important to note that there is a high incidence of lower respiratory infections in children in LMIC regardless of HIV status.

There is a paucity of well-described or large studies in children compared to in adults. There was significant heterogeneity in the studies included in the review, and few studies reported important confounding factors such as use of co-trimoxazole prophylaxis, age at ART initiation and CD4 count. Also, regional differences could not be examined due to a limited number of studies in Latin America and Asia.

Notwithstanding these limitations, ART has resulted in a substantial cost-saving due to the numbers of OIs averted by use of ART. The 2015 WHO guidelines now recommend ART initiation in all children and this is likely to have an even larger impact on the incidence of OIs and mortality. Along with this, strategies to reduce the burden of TB and pneumonia in children are urgently needed.

A hybrid mobile approach for population-wide HIV testing in rural east Africa: an observational study.


Background: Despite large investments in HIV testing, only an estimated 45% of HIV-infected people in sub-Saharan Africa know their HIV status. Optimum methods for maximising population-level testing remain unknown. We sought to show the effectiveness of a hybrid mobile HIV testing approach at achieving population-wide testing coverage.

Methods: We enumerated adult (≥15 years) residents of 32 communities in Uganda (n=20) and Kenya (n=12) using a door-to-door census. Stable residence was defined as living in the community for at least 6 months in the past year. In each community, we did 2 week multiple-disease community health campaigns (CHCs) that included HIV testing, counselling, and referral to care if HIV infected; people who did not participate in the CHCs were approached for home-based testing (HBT) for 1-2 months within the 1-6 months after the CHC. We measured population HIV testing coverage and predictors of testing via HBT rather than CHC and non-testing.

Findings: From April 2, 2013, to June 8, 2014, 168 772 adult residents were enumerated in the door-to-door census. HIV testing was achieved in 131 307 (89%) of 146 906 adults with stable residence. 13 043 of 136 033 (9.6%, 95% CI 9.4-9.8) adults with and without stable residence had
HIV; median CD4 count was 514 cells per µL (IQR 355-703). Among 131,307 adults with stable residence tested, 56,106 (43%) reported no previous testing. Among 13,043 HIV-infected adults, 4,932 (38%) were unaware of their status. Among 105,170 CHC attendees with stable residence tested, 104,635 (80%; range 60-93% across communities) tested via CHCs. In multivariable analyses of adults with stable residence, predictors of non-testing included being male (risk ratio [RR] 1.52, 95% CI 1.48-1.56), single marital status (1.70, 1.66-1.75), age 30-39 years (1.58, 1.52-1.65 vs 15-19 years), residence in Kenya (1.46, 1.41-1.50), and migration out of the community for at least 1 month in the past year (1.60, 1.53-1.68). Compared with unemployed people, testing for HIV was more common among farmers (RR 0.73, 95% CI 0.67-0.79) and students (0.73, 0.69-0.77); and compared with people with no education, testing was more common in those with primary education (0.84, 0.80-0.89).

Interpretation: A hybrid, mobile approach of multiple-disease CHCs followed by HBT allowed for flexibility at the community and individual level to help reach testing coverage goals. Men and mobile populations remain challenges for universal testing.

Abstract access

Editor’s notes: Achieving high levels of HIV testing coverage remains a challenge in many parts of sub-Saharan Africa. Conventional facility-based HIV testing models are insufficient to achieve the UNAIDS 90-90-90 targets and maximise the prevention benefits of treatment. This study was able to achieve extremely high levels of HIV testing coverage in a short period of time by strategically combining two community-based testing approaches. By offering testing through multiple-disease community health campaigns (CHC), followed by focused home-based testing (HBT) for individuals who did not attend the CHCs, nearly 90% of adult stable residents accepted HIV testing. This near-universal coverage was achieved in all 32 communities (range 84%-95%) across two countries, in a variety of settings with different rates of HIV prevalence and of previous testing. Testing uptake in the CHCs varied considerably across the communities (52%-82%), demonstrating the value of this hybrid approach to expand coverage. Non-stable residents, who were 13% of the population, had low rates of testing uptake (22%). High rates of mobility remain a particular challenge for universal HIV testing coverage, and additional strategies are necessary to engage this group. A potential limitation of a focused approach to HBT is the need for community enumeration. Still the results illustrate that achieving high HIV testing coverage is feasible with a combination of community-based approaches.

Progress in reversing the HIV epidemic through intensified access to antiretroviral therapy: results from a nationally representative population-based survey in Kenya, 2012.


Background: In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) called for 90% of people living with HIV (PLHIV) to know their status, 90% of these to be on antiretroviral therapy (ART), and 90% of these to be virally suppressed by 2020 (90-90-90). It is not clear whether planned ART scale-up in countries whose eligibility criteria for ART initiation are based on recommendations from the 2013 World Health Organization treatment guidelines will be sufficient to meet UNAIDS’ new global targets.

Materials and methods: Using data from a nationally representative population-based household survey of persons in Kenya we compared coverage and unmet need associated with HIV diagnosis, ART, and viral suppression among PLHIV aged 15-64 years in 2012 based on
criteria outlined in the 2014 national ART guidelines and UNAIDS' 90-90-90 goals. Estimates
were weighted to account for sampling probability and nonresponse.

Results: **Eight in ten PLHIV aged 15-64 years needed ART based on treatment eligibility.** Need
for treatment based on the national treatment policy was 97.4% of treatment need based on UNAIDS' 90-90-90 goals, requiring an excess of 24 000 PLHIV to access treatment beyond those eligible for
ART to achieve UNAIDS' 90-90-90 treatment target. The gap in treatment coverage was high,
ranging from 43.1% nationally to 52.3% in Nyanza among treatment-eligible PLHIV and 44.6% nationally to 52.4% in Nyanza among all PLHIV.

Conclusion: **Maintaining the current pace of ART scale-up in Kenya will result in thousands of PLHIV unreach**ed, many with high viral load and at-risk of transmitting infection to others. Careful
strategies for reaching 90-90-90 will be instrumental in determining whether intensified access to
treatment can be achieved to reach all who require ART.

**Abstract** Full-text [free] access

**Editor’s notes:** The HIV field is pushing for aggressive scale-up of programmes to stem the HIV
epidemic. In this regard, UNAIDS launched the 90-90-90 targets to motivate countries to increase
awareness, testing and treatment of people living with HIV. This paper presents an analysis of data
collected through the last national Kenya AIDS Indicator Survey (KAIS) which examines the number of
people reached with testing and treatment in 2012 as compared with the 90-90-90 targets which
the country adopted in 2014. The analysis illustrates that the scale up of testing and treatment will
need to dramatically increase to meet the targets. The paper notes the importance of strategizing how
best to reach the populations most affected. In Kenya’s case, a geographic approach to scaling up in
higher incidence areas is now being implemented. Within the geographical approach, strategies
include testing family members of people living with HIV, and community-based testing strategies
(such as home-based testing and counselling and self-testing), delivered in settings with high HIV
prevalence. Analyses such as the one presented in this paper can help other countries in similar
situations to review how best to apply limited resources in order to meet targets.

2. **Elimination of childhood infections**

Comparative cost-effectiveness of Option B+ for prevention of mother-to-child transmission of
HIV in Malawi.

doi: 10.1097/QAD.0000000000001009.

Objective: **To estimate the cost-effectiveness of prevention of mother-to-child transmission
(MTCT) of HIV with lifelong antiretroviral therapy (ART) for pregnant and breastfeeding women
('Option B+') compared with ART during pregnancy or breastfeeding only unless clinically
indicated ('Option B').**

Design: Mathematical modelling study of first and second pregnancy, informed by data from the
Malawi Option B+ programme.

Methods: **Individual-based simulation model. We simulated cohorts of 10 000 women and their infants
during two subsequent pregnancies, including the breastfeeding period, with either Option B+ or B.** We parameterized the model with data from the literature and by analysing
programmatic data. We compared total costs of antenatal and postnatal care, and lifetime costs and disability-adjusted life-years of the infected infants between Option B+ and Option B.

Results: During the first pregnancy, 15% of the infants born to HIV-infected mothers acquired the infection. With Option B+, 39% of the women were on ART at the beginning of the second pregnancy, compared with 18% with Option B. For second pregnancies, the rates MTCT were 11.3% with Option B+ and 12.3% with Option B. The incremental cost-effectiveness ratio comparing the two options ranged between about US$ 500 and US$ 1300 per DALY averted.

Conclusion: Option B+ prevents more vertical transmissions of HIV than Option B, mainly because more women are already on ART at the beginning of the next pregnancy. Option B+ is a cost-effective strategy for PMTCT if the total future costs and lost lifetime of the infected infants are taken into account.

Abstract access

Editor’s notes: Nearly a quarter of a million children acquire HIV from their mothers every year. Antiretroviral therapy (ART) in pregnant women greatly reduces the risk of mother-to-child HIV transmission to less than two percent. Malawi was the first country to introduce ‘Option B+’, a programme eliminating new HIV infections among children and keeping their mothers alive, in which all pregnant and breastfeeding women living with HIV start lifelong ART regardless of CD4 count or clinical staging. This study compares the cost-effectiveness of Option B+ in Malawi, with Option B, in which ART is recommended only for the duration of pregnancy or breastfeeding, unless the woman qualifies for ART for her own health. Both options have been recommended by World Health Organisation prevention of mother-to-child HIV transmission strategies.

The model simulated a cohort of 10 000 women pregnant for the first time, from conception to the time when the infants were two years old. The authors found that although the total costs of implementing Option B+ were higher than those of Option B, the former can reduce the costs of HIV care and treatment in the future by preventing new infections. The incremental cost-effectiveness ratio of Option B+ compared to Option B, ranged from USD 500 to USD 1300 per disability-adjusted life-years averted, depending on key assumptions around survival and care. The results support the implementation of Option B+ as it is likely to be a cost-effective strategy in the long term and the authors suggest it should be considered as the preferred strategy in low-income, high-fertility settings.

Like all models, this model has some limitations. It only considers women’s first two pregnancies, but the fertility rate in Malawi is high (5.5 births per woman). The model limits itself to mother-to-child HIV transmission, and does not take into account sexual transmission, which is likely to be lower in Option B+. Further research in these two areas would be worthwhile. The landscape is quickly changing, as World Health Organization guidelines now suggest testing and treatment strategies. However, until that policy is fully implemented and absorbed across the world, Option B+ will remain a key element in the HIV response.

3. Combination prevention

Perspectives on intimate relationships among young people in rural South Africa: the logic of risk.

This paper explores how young people in rural South Africa understand gender, dating, sexuality and risk-taking in adolescence. The empirical material drawn upon consists of 20 interviews with young men and women (aged 18-19) and reflects normative gender patterns characterised by compulsory heterosexuality and dating as obligatory, and representing key symbols of normality. However, different meanings of heterosexual relationships are articulated in the interviews, for example in the recurring concept of 'passing time', and these meanings show that a relationship can be something arbitrary: a way to reduce boredom and have casual sex. Such a rationale for engaging in a relationship reflects one of several other normative gender patterns, which relate to the trivialisation of dating and sexual risk-taking, and which entail making compromises and legitimising deviations from the 'ideal' life-script and the hope of a better future. However, risks do not exclusively represent something bad, dangerous or immoral, because they are also used as excuses to avoid sex, HIV acquisition and early pregnancy. In conclusion, various interrelated issues can both undermine and/or reinforce risk awareness and subsequent risk behaviour. Recognition of this tension is essential when framing policies to support young people to reduce sexual risk-taking behaviour.

Abstract access

Editor's notes: This article explores how young people in a poor, rural area in South Africa articulate and understand gender, dating, sexuality, and risk-taking. Twenty young people (10 female, 10 male) aged between 18 and 19 years of age were randomly selected from three villages that participate in the Health and Socio-Demographic Surveillance System in Mpumalanga Province in north-eastern South Africa.

Participants’ narratives highlight how normative gender patterns characterised by compulsory heterosexuality and dating as obligatory represent key symbols of normality. The authors highlight how two themes, early pregnancy and HIV, are central to understanding practices of dating and heterosexual relationships. They are also important for understanding ideas about the consequences of a dissolute lifestyle and the risk it exerts on plans and hopes for a better future. This risk was perceived to be particularly acute by, and for, young women who are seen to bear the brunt of negative outcomes, particularly relating to early school dropout.

The findings of this study have important implications for HIV prevention programmes, particularly for adolescent girls and young women. Where intimate relationships are trivialised as guided by normative gender patterns and pressure to have heterosexual relationships, young people risk becoming infected with HIV, becoming parents too early, and interrupting their education. The findings highlight the potential for context-sensitive programmes which play careful attention to local norms and young people’s internalised relationship discourses. These could usefully include opportunities for critical reflection in order to support young people to reduce their exposure to risks. It is also important to recognise young people’s aspirations, and the perceived benefits they derive from relationships.

The male factor: outcomes from a cluster randomized field experiment with a couples-based HIV prevention intervention in a South African township.


Background: This study examined the effects of the Couples Health CoOp intervention on heavy drinking, condom use, and HIV incidence.
Methods: Thirty neighborhoods from one South African township were cluster randomized into three intervention arms: Couples Health CoOp (CHC), Women's Health CoOp/Men's Health CoOp (WHC/MHC), or a comparison arm. We recruited 290 men from informal drinking establishments who reported drinking alcohol regularly. We also recruited their main heterosexual sex partners.

Results: At 6-month follow-up, men in the CHC arm were less likely to report heavy drinking (OR 0.47, 95% CI: 0.25, 0.90) and were more likely to report consistent condom use during the past month (OR 2.66, 95% CI: 1.23, 5.76) than men in the comparison arm. At baseline, 26% of women and 13% of men were HIV-infected; at 6-month follow-up, 16 females and 5 males had seroconverted. HIV incidence was significantly lower among women in the CHC arm (IRR 0.22, 95% CI: 0.04, 1.01) than in the WHC/MHC arm.

Conclusions: A couples-based intervention focusing on intersecting risks for HIV can improve bio-behavioral outcomes, underscoring the importance of engaging couples together in HIV prevention.

Abstract access

Editor’s notes: This study describes the benefits of a novel couples-based programme that addresses key drivers of HIV incidence in South Africa. It focuses on the intersection of alcohol use, relationship contexts, and gender norms. Heavy drinking among men in South Africa is associated with HIV risks including multiple concurrent sexual partnerships and low rates of condom use. In addition, heavy drinking alongside gender norms that disempower women can lead to increased HIV risk for female partners. For example, women may seek sexual partners outside of their main relationship for money, due to male regular partners spending household income on alcohol instead. The study extends the Women’s Health CoOp (an evidence-based programme to reduce substance use, violence, and sexual risks among vulnerable women) to include both partners. The hypothesis is that a programme addressing both partners together (the Couples Health CoOp [CHC] arm) would be more effective than the original female-focused programme at reducing alcohol use and risk behaviors. They found that men reported reduced heavy drinking in all three arms including the control arm after six months (compared to baseline) and the reduction in heavy drinking was greatest in the CHC arm. This highlights the role of couples-based programmes for HIV prevention in women. The high HIV incidence in this setting (16 per 100 person-years in women; 4 per 100 person-years in men) is a reminder that innovative activities are necessary. Future work should continue to include exploration of the effectiveness of adapting of single-gender programmes to be couple-based.

Developing family interventions for adolescent HIV prevention in South Africa.


Adolescents and young people account for 40% of all new HIV infections each year, with South Africa one of the hardest hit countries, and having the largest population of people living with HIV. Although adolescent HIV prevention has been delivered through diverse modalities in South Africa, and although family-based approaches for adolescent HIV prevention have great potential for highly affected settings such as South Africa, there is a scarcity of empirically tested family-based adolescent HIV preventive interventions in this setting. We therefore conducted focus groups and in-depth interviews with key informants including clinicians, researchers, and other individuals representing organizations providing HIV and related health services to adolescents and parents (N = 82). We explored family perspectives and interactions around topics such as communication
about sex, HIV, and relationships. Participants described aspects of family interactions that presented both challenges and opportunities for family-based adolescent HIV prevention. Parent-child communication on sexual topics were taboo, with these conversations perceived by some adults as an invitation for children to engage in HIV risk behavior. Parents experienced social sanctions for discussing sex and adolescents who asked about sex were often viewed as disrespectful and needing discipline. However, participants also identified context-appropriate strategies for addressing family challenges around HIV prevention including family meetings, communal parenting, building efficacy around parent-adolescent communication around sexual topics, and the need to strengthen family bonding and positive parenting. Findings indicate the need for a family intervention and identify strategies for development of family-based interventions for adolescent HIV prevention. These findings will inform design of a family intervention to be tested in a randomized pilot trial.

Abstract Full-text [free] access

Editor’s notes: This short paper presents a qualitative study about family discussions about HIV and sex in Khayelitsha, South Africa. The results illustrate that sex is considered by many adults a taboo subject with adolescents younger than 18 years old. Young people who initiate discussion about sex, HIV risk or pregnancy can be scolded for being disrespectful. Sex is often discussed as a problem after young people have already started being sexually active. Study participants identified ‘family conferences’, with parents but also relatives more broadly, as promising settings for programmes. The activities should facilitate discussions that frame communication about sex and HIV prevention as positive.

4. Key populations

The Silk Road health project: how mobility and migration status influence HIV risks among male migrant workers in central Asia.


Objectives: We examined whether mobility, migrant status, and risk environments are associated with sexually transmitted infections (STIs) and HIV risk behaviors (e.g. sex trading, multiple partners, and unprotected sex).

Methods: We used Respondent Driven Sampling (RDS) to recruit external male migrant market vendors from Kyrgyzstan, Uzbekistan, and Tajikistan as well as internal migrant and non-migrant market vendors from Kazakhstan. We conducted multivariate logistic regressions to examine the effects of mobility combined with the interaction between mobility and migration status on STIs and sexual risk behaviors, when controlling for risk environment characteristics.

Results: Mobility was associated with increased risk for biologically-confirmed STIs, sex trading, and unprotected sex among non-migrants, but not among internal or external migrants. Condom use rates were low among all three groups, particularly external migrants. Risk environment factors of low-income status, debt, homelessness, and limited access to medical care were associated with unprotected sex among external migrants.
Conclusion: Study findings underscore the role mobility and risk environments play in shaping HIV/STI risks. They highlight the need to consider mobility in the context of migration status and other risk environment factors in developing effective prevention strategies for this population.

Abstract Full-text [free] access

**Editor’s notes:** The 14 participants selected as seeds in this respondent driven sampling (RDS) strategy generated two large chains that made up 90% of the recruited study sample of 1324 male labour market workers at the Baraholka Market in Almaty, Kazakhstan. An estimated one million labour migrants enter Kazakhstan each year from neighbouring Central Asian countries that lack employment opportunities. However they face stigma, discrimination, police harassment, and lack of access to services. Finding out whether they are resilient to risk of exposure to HIV and other sexually transmitted infections (STIs) or are more likely to acquire HIV/STIs is key to designing effective HIV prevention strategies in a country that saw HIV incidence rise 25% between 2001 and 2009. This study looked at associations between HIV and STI risk and mobility – defined as having travelled outside Almaty in the last 90 days. The study was among three groups at the market: external migrants, internal migrants, and non-migrants. The analysis adjusted for both sociodemographic and structural risk environment factors (legal status, income, debt, policing, homelessness, loneliness, social support, access to medical care, and alcohol use). Overall, 5.2% were positive for any STI. These included 2.1% of external migrants, 7.5% of internal migrants, and 8.8% of non-migrants. The authors hypothesise that mobility was not associated with increased STIs and a range of risk behaviours in external and internal migrants because these men travel primarily to visit their families and because they are goal-oriented and focused on fulfilling their roles as major wage earners for their families. These findings are in contrast to those of other studies that suggest that migrants are at higher HIV risk and challenge perceptions of migrants as a source of disease transmission within host countries. They underscore the importance of prevention strategies in unique venues such as markets, including peer-led prevention messaging, mobile clinics, and confidential HIV/STI testing. However, to address the factors that put migrants at risk for HIV, the authors argue for labour agreements, a legal registration process, and other measures to sustain their rights, prevent violence against migrants, and reduce marginalisation.

How effective is help on the doorstep? A longitudinal evaluation of community-based organisation support.


Community-based responses have a lengthy history. The ravages of HIV on family functioning has included a widespread community response. Although much funding has been invested in front line community-based organisations (CBO), there was no equal investment in evaluations. This study was set up to compare children aged 9-13 years old, randomly sampled from two South African provinces, who had not received CBO support over time (YC) with a group of similarly aged children who were CBO attenders (CCC). YC baseline refusal rate was 2.5% and retention rate was 97%. CCC baseline refusal rate was 0.7% and retention rate was 86.5%. 1848 children were included—446 CBO attenders compared to 1402 9-13 year olds drawn from a random sample of high-HIV prevalence areas. Data were gathered at baseline and 12-15 months follow-up. Standardised measures recorded demographics, violence and abuse, mental health, social and educational factors. Multivariate regression analyses revealed that children attending CBOs had lower odds of experiencing weekly domestic conflict between adults in their home (OR 0.17;
95% CI 0.09, 0.32), domestic violence (OR 0.22; 95% CI 0.08, 0.62), or abuse (OR 0.11; 95% CI 0.05, 0.25) at follow-up compared to participants without CBO contact. CBO attenders had lower odds of suicidal ideation (OR 0.41; 95% CI 0.18, 0.91), fewer depressive symptoms (B = -0.40; 95% CI -0.62, -0.17), less perceived stigma (B = -0.37; 95% CI -0.57, -0.18), fewer peer problems (B = -1.08; 95% CI -1.29, -0.86) and fewer conduct problems (B = -0.77; 95% CI -0.95, -0.60) at follow-up. In addition, CBO contact was associated with more prosocial behaviours at follow-up (B = 1.40; 95% CI 1.13, 1.67). No associations were observed between CBO contact and parental praise or post-traumatic symptoms. These results suggest that CBO exposure is associated with behavioural and mental health benefits for children over time. More severe psychopathology was not affected by attendance and may need more specialised input.

Abstract  Full-text [free] access

Editor’s notes: This study is novel in both its research question and its methodology. The study aims to assess whether receipt of support from community-based organisations (CBOs) impacts the mental and social well-being of children in high HIV prevalence areas. The CBOs studied include many different organisations with diverse services, giving the study the benefit of assessing the overall impact of a combination of small, motivated groups. This helps lend credibility to CBOs and to convince policymakers and funders to support small-scale CBOs.

In terms of methodology, the study utilises two longitudinal datasets from southern Africa to explore the study aims. One survey is from a study of children affected by HIV served by CBOs, while the other is from a study of children affected by HIV without CBO support. There are some limitations to using two different studies, most especially unclear comparability and, in this case, lack of control data to adjust for possible differences, for example on socio-economic status or how HIV specifically affected the child. Despite these, this paper has striking results, and is an innovative effort to improve our understanding of the impact of CBOs on children’s well-being and should spur further creativity in impact evaluation methods.

Heterogeneity among sex workers in overlapping HIV risk interactions with people who inject drugs: a cross-sectional study from 8 major cities in Pakistan.


Concerns remain regarding the heterogeneity in overlapping human immunodeficiency virus (HIV) risk behaviors among sex workers (SWs) in Pakistan; specifically, the degree to which SWs interact with people who inject drugs (PWID) through sex and/or needle sharing. Following an in-depth mapping performed in 2011 to determine the size and distribution of key populations at highest risk of HIV acquisition in Pakistan, a cross-sectional biological and behavioral survey was conducted among PWID, female (FSWs), male (MSWs), and hijra/transgender (HSWs) sex workers, and data from 8 major cities were used for analyses. Logistic regression was used to identify factors, including city of residence and mode of SW-client solicitation, contributing to the overlapping risks of drug injection and sexual interaction with PWID. The study comprised 8483 SWs (34.5% FSWs, 32.4% HSWs, and 33.1% MSWs). Among SWs who had sex with PWID, HSWs were 2.61 (95% confidence interval [CI], 1.19-5.74) and 1.99 (95% CI, 0.94-4.22) times more likely to inject drugs than MSWs and FSWs, respectively. There was up to a 3-fold difference in drug injecting probability, dependent on where and/or how the SW solicited clients. Compared with SWs in Larkana, the highest likelihood of drug injection use was among SWs in Multan (OR = 4.52; 95% CI: 3.27-6.26), followed by those in Lahore, Quetta, and Faisalabad. Heterogeneity exists in the
overlapping patterns of HIV risk behaviors of SWs. **The risk of drug injection among SWs also varies by city.** Some means of sexual client solicitation may be along the pathway to overlapping HIV risk vulnerability due to increased likelihood of drug injection among SWs. There is a need to closely monitor the mixing patterns between SWs and PWID and underlying structural factors, such as means of sexual client solicitation, that mediate HIV risk, and implement prevention programs customized to local sub-epidemics.

Abstract Full-text [free] access

**Editor’s notes:** This is an important paper reporting findings of an HIV prevalence and risk behaviour survey among sex workers and people who inject drugs. The paper describes the diversity of sex work, including male and transgender sex workers that are often neglected in research and service planning. It also examines injecting drug use among sex workers, a behaviour that can increase sex workers’ vulnerability to HIV, violence and other health harms. The finding that among sex workers who had a sex partner who also injected drugs, transgender sex workers had higher odds of injecting than male or female sex workers is important. This finding highlights the differences in vulnerability among the three sex worker populations, whose diversity is often not taken into account in programme planning. Other international evidence suggests increased stigma experienced by transgender sex workers on account of their gender. For example, with increased arrest and harassment administered by police and higher levels of poor emotional health. These are factors that might explain use of injecting drugs as a coping strategy. The study illustrates a clear need to target harm reduction services among this population, to ensure they have access to needle-syringe programmes. Advice on safe injecting practices and how to manage injecting drug use alongside sex work are also necessary. Findings also clearly illustrate the need to understand better the underlying determinants of drug use and address those. Understanding why prevalence of drug use varies by city is vital. So too, is understanding how the way in which clients are engaged increases risk of injecting, in order to create enabling environments to minimise harms associated with injecting.

5. Elimination of gender inequalities

**Perceived impact of a land and property rights program on violence against women in rural Kenya: a qualitative investigation.**


The current study focuses on a community-led land and property rights program in two rural provinces in western Kenya. **The program was designed to respond to women’s property rights violations to reduce violence against women and HIV risks at the community level.** Through in-depth interviews with 30 women, we examine the perceived impact that this community-level property rights program had on violence against women at the individual and community level. We also examine perceptions as to how reductions in violence were achieved. Finally, we consider how our findings may aid researchers in the design of structural violence-prevention strategies.

Abstract access

**Editor’s notes:** This paper reports on women's experiences of violence following reporting of disinheritance to a community-led property rights violations programme in Kenya. The research was set in two rural districts in Kenya, where HIV prevalence is high (23.8-33%) and property rights
violations are common. Interviews were conducted with women who participated in GROOTS-Kenya’s Community Land and Property Watch Dog Model (CWDG). This model is comprised of volunteer women and men. These people monitor women’s disinheritance locally and mediate land disputes. They also refer unresolved cases to formal adjudication mechanisms and raise awareness about women’s rights.

The researchers found that for nearly all of the women, violence ceased immediately on reporting cases of violent disinheritance to the CWDG. The presence of the CWDG led to a broader reduction in sexual and domestic violence against women at the community level. The women explained that this was for four reasons: (a) improved individual- and community-level knowledge about women’s rights/improved knowledge about violence against women, (b) the existence of a community-based mechanism for reporting cases of violence, (c) the responsiveness of the CWDG to cases of violence, and (d) fears that perpetrators had about the legal consequences of perpetrating violence. This research contributes to a growing body of evidence that addressing structural factors such as economic empowerment is important. However, there is a need to strengthen this approach through providing women with property rights. Property rights may empower women more than other economic empowerment approaches such as micro-finance.

6. Financing


Objectives: To estimate the present value of current and future funding needed for HIV treatment and prevention in 9 sub-Saharan African (SSA) countries that account for 70% of HIV burden in Africa under different scenarios of intervention scale-up. To analyse the gaps between current expenditures and funding obligation, and discuss the policy implications of future financing needs.

Design: We used the Goals module from Spectrum, and applied the most up-to-date cost and coverage data to provide a range of estimates for future financing obligations. The four different scale-up scenarios vary by treatment initiation threshold and service coverage level. We compared the model projections to current domestic and international financial sources available in selected SSA countries.

Results: In the 9 SSA countries, the estimated resources required for HIV prevention and treatment in 2015-2050 range from US$98 billion to maintain current coverage levels for treatment and prevention with eligibility for treatment initiation at CD4 count of <500/mm³ to US$261 billion if treatment were to be extended to all HIV-positive individuals and prevention scaled up. With the addition of new funding obligations for HIV—which arise implicitly through commitment to achieve higher than current treatment coverage levels—overall financial obligations (sum of debt levels and the present value of the stock of future HIV funding obligations) would rise substantially.

Conclusions: Investing upfront in scale-up of HIV services to achieve high coverage levels will reduce HIV incidence, prevention and future treatment expenditures by realising long-term preventive effects of ART to reduce HIV transmission. Future obligations are too substantial for most SSA countries to be met from domestic sources alone. New sources of funding, in addition to domestic sources, include innovative financing. Debt sustainability for sustained HIV response is an urgent imperative for affected countries and donors.
Abstract  Full-text [free] access

Editor’s notes: The authors of this interesting paper use the most up-to-date cost and coverage data to provide a range of estimates for future treatment financing obligations. Epidemiological parameters are included to fit the Goals model and key prevention services such as ‘prevention of mother-to-child HIV transmission’ and ‘voluntary medical male circumcision’ are also included.

Financing needs for the nine countries are estimated by varying treatment initiation threshold (everyone initiated on treatment versus initiation at CD4 of <500cells/mm³) and/or coverage level for prevention and treatment (‘current’ levels and a ‘scale up’ scenario). The authors also attempt to assess both the ethics and the cost of different approaches.

For all scenarios, there is a steady decline in proportion of treatment costs and an increase in the proportion of prevention costs. This apparent contradiction is largely because there will be fewer individuals on treatment over time but prevention costs rise because they are mostly invested in non-infected populations, which increases with population growth.

In the nine countries, estimated resources required for HIV prevention and treatment from 2015-2050 will be large. This is increased further when human resources and supplies increase at the rate of GDP per capita.

However, there is undoubtedly an ethical responsibility to not only continue financing people receiving ART, but, that the responsibility extends to people in equal need who are not on treatment. The ethics is underpinned by the evidence. This illustrates how ‘front-loading’ investments in HIV scale-up now to ensure high levels of coverage, will significantly reduce future HIV incidence and prevalence.

7. Health systems and services

Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial.


Background: HIV-associated tuberculosis is difficult to diagnose and results in high mortality. Frequent extra-pulmonary presentation, inability to obtain sputum, and paucibacillary samples limits the usefulness of nucleic-acid amplification tests and smear microscopy. We therefore assessed a urine-based, lateral flow, point-of-care, lipoarabinomannan assay (LAM) and the effect of a LAM-guided anti-tuberculosis treatment initiation strategy on mortality.

Methods: We did a pragmatic, randomised, parallel-group, multicentre trial in ten hospitals in Africa--four in South Africa, two in Tanzania, two in Zambia, and two in Zimbabwe. Eligible patients were HIV-positive adults aged at least 18 years with at least one of the following symptoms of tuberculosis (fever, cough, night sweats, or self-reported weight loss) and illness severity necessitating admission to hospital. Exclusion criteria included receipt of any anti-tuberculosis medicine in the 60 days before enrolment. We randomly assigned patients (1:1) to either LAM plus routine diagnostic tests for tuberculosis (smear microscopy, Xpert-MTB/RIF, and culture; LAM group) or routine diagnostic tests alone (no LAM group) using computer-generated allocation lists in blocks of ten. All patients were asked to provide a urine sample of at least 30 mL.
at enrolment, and trained research nurses did the LAM test in patients allocated to this group using the Alere Determine tuberculosis LAM Ag lateral flow strip test (Alere, USA) at the bedside on enrolment. On the basis of a positive test result, the nurses made a recommendation for initiating anti-tuberculosis treatment. The attending physician made an independent decision about whether to start treatment or not. Neither patients nor health-care workers were masked to group allocation and test results. The primary endpoint was 8-week all-cause mortality assessed in the modified intention-to-treat population (those who received their allocated intervention). This trial is registered with ClinicalTrials.gov, number NCT01770730.

Findings: Between Jan 1, 2013, and Oct 2, 2014, we screened 8728 patients and randomly assigned 2659 to treatment (1336 to LAM, 1323 to no LAM). 108 patients did not receive their allocated treatment, mainly because they did not meet the inclusion criteria, and 23 were excluded from analysis, leaving 2528 in the final modified intention-to-treat analysis (1257 in the LAM group, 1271 in the no LAM group). Overall all-cause 8-week mortality occurred in 578 (23%) patients, 261 (21%) in LAM and 317 (25%) in no LAM, an absolute reduction of 4% (95% CI 1-7). The risk ratio adjusted for country was 0.83 (95% CI 0.73-0.96), p=0.012, with a relative risk reduction of 17% (95% CI 4-28). With the time-to-event analysis, there were 159 deaths per 100 person-years in LAM and 196 per 100 person-years in no LAM (hazard ratio adjusted for country 0.82 [95% CI 0.70-0.96], p=0.015). No adverse events were associated with LAM testing.

Interpretation: Bedside LAM-guided initiation of anti-tuberculosis treatment in HIV-positive hospital inpatients with suspected tuberculosis was associated with reduced 8-week mortality. The implementation of LAM testing is likely to offer the greatest benefit in hospitals where diagnostic resources are most scarce and where patients present with severe illness, advanced immunosuppression, and an inability to self-expectorate sputum.

Abstract access

Editor’s notes: TB is a leading cause of hospitalization and in-hospital death among people living with HIV worldwide. This randomised controlled trial in southern Africa provides strong evidence of the impact of a simple, urine-based test in HIV-positive adults admitted to hospital with symptoms of TB. Use of the lateral flow lipoarabinomannan (LAM) test, in addition to a package of routine TB diagnostic tests, led to a modest reduction in all-cause mortality. This reduction in mortality occurred despite only a small increase in the proportion starting TB treatment, suggesting that LAM testing might have enabled more precision in the identification of people with TB.

Half of all deaths occurred in people with CD4 cell count ≤50 cells/µL and the impact of the urinary LAM test was greatest in this group, as suggested by previous studies. This may lead to strengthening of WHO policy recommendations to use the lateral flow LAM test to assist with TB diagnosis in people admitted to hospital with advanced HIV and with symptoms and signs of TB. There is still no strong evidence to suggest a role for LAM testing at more peripheral levels of the health system or in people who are not seriously ill.

The heterogeneity in effect between countries is notable, although the trial was not powered to detect mortality differences at each site. The availability and use of other diagnostics (which could include sputum smear microscopy, Xpert®, chest X-ray, ultrasound and computed tomography), and the level of physician input in clinical management, differed substantially across sites and could have modified the effect of LAM testing. Additional exploration of data from this trial and from other ongoing studies should help to further define the role of urine LAM in the TB diagnostic bundle in different health care settings.
Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial.


Background: Mortality within the first 6 months after initiating antiretroviral therapy is common in resource-limited settings and is often due to tuberculosis in patients with advanced HIV disease. Isoniazid preventive therapy is recommended in HIV-positive adults, but subclinical tuberculosis can be difficult to diagnose. We aimed to assess whether empirical tuberculosis treatment would reduce early mortality compared with isoniazid preventive therapy in high-burden settings.

Methods: We did a multicountry open-label randomised clinical trial comparing empirical tuberculosis therapy with isoniazid preventive therapy in HIV-positive outpatients initiating antiretroviral therapy with CD4 cell counts of less than 50 cells per µL. Participants were recruited from 18 outpatient research clinics in ten countries (Malawi, South Africa, Haiti, Kenya, Zambia, India, Brazil, Zimbabwe, Peru, and Uganda). Individuals were screened for tuberculosis using a symptom screen, locally available diagnostics, and the GeneXpert® MTB/RIF assay when available before inclusion. Study candidates with confirmed or suspected tuberculosis were excluded. Inclusion criteria were liver function tests 2.5 times the upper limit of normal or less, a creatinine clearance of at least 30 mL/min, and a Karnofsky score of at least 30. Participants were randomly assigned (1:1) to either the empirical group (antiretroviral therapy and empirical tuberculosis therapy) or the isoniazid preventive therapy group (antiretroviral therapy and isoniazid preventive therapy). The primary endpoint was survival (death or unknown status) at 24 weeks after randomisation assessed in the intention-to-treat population. Kaplan-Meier estimates of the primary endpoint across groups were compared by the z-test. All participants were included in the safety analysis of antiretroviral therapy and tuberculosis treatment. This trial is registered with ClinicalTrials.gov, number NCT01380080.

Findings: Between Oct 31, 2011, and June 9, 2014, we enrolled 850 participants. Of these, we randomly assigned 424 to receive empirical tuberculosis therapy and 426 to the isoniazid preventive therapy group. The median CD4 cell count at baseline was 18 cells per µL (IQR 9-32). At week 24, 22 (5%) participants from each group died or were of unknown status (95% CI 3.5-7.8) for empirical group and for isoniazid preventive therapy (95% CI 3.4-7.8); absolute risk difference of -0.06% (95% CI -3.05 to 2.94). Grade 3 or 4 signs or symptoms occurred in 50 (12%) participants in the empirical group and 46 (11%) participants in the isoniazid preventive therapy group. Grade 3 or 4 laboratory abnormalities occurred in 99 (23%) participants in the empirical group and 97 (23%) participants in the isoniazid preventive therapy group.

Interpretation: Empirical tuberculosis therapy did not reduce mortality at 24 weeks compared with isoniazid preventive therapy in outpatient adults with advanced HIV disease initiating antiretroviral therapy. The low mortality rate of the trial supports implementation of systematic tuberculosis screening and isoniazid preventive therapy in outpatients with advanced HIV disease.

Abstract access
**Editor’s notes:** Tuberculosis (TB) remains the leading cause of death among HIV-positive people worldwide. Existing diagnostic tests for TB lack sensitivity, particularly among HIV-positive people, and autopsy studies consistently illustrate that TB is common at death, but often not identified prior to death. This has led to questions about whether empirical TB treatment, meaning treatment for TB in the absence of bacteriological confirmation, should be more widely used among HIV-positive people.

This trial compared empirical TB treatment to isoniazid preventive therapy among adult outpatients with very low CD4 counts starting antiretroviral therapy (ART). People could be enrolled in the study if they did not have confirmed or suspected TB based on symptoms, locally-accessible diagnostic tests (including chest radiography and sputum smear) and, when available, testing with Xpert® MTB/RIF. There was no difference in mortality at six months between participants given empirical TB treatment compared to isoniazid preventive therapy. Mortality was remarkably low overall, particularly considering that participants had very low CD4 counts. It seems likely that the enrolment criteria excluded people at highest risk of death from participating in the study.

Screening for TB at the time of starting ART could reduce mortality if the tests are sufficiently sensitive, and if people identified to have TB receive effective treatment. However, this study was not designed to address how best to do this in resource-limited settings, where chest radiography and Xpert® MTB/RIF are often not accessible. This study does suggest that isoniazid preventive therapy can be given at the time of ART initiation among people who have been effectively screened for TB. The results of other studies of empirical TB treatment, with different designs in different populations, are awaited. Data from all these studies together may provide evidence to guide the optimal package of care for people presenting with advanced HIV disease.

**Tuberculosis-related mortality in people living with HIV in Europe and Latin America: an international cohort study.**


Background: Management of tuberculosis in patients with HIV in eastern Europe is complicated by the high prevalence of multidrug-resistant tuberculosis, low rates of drug susceptibility testing, and poor access to antiretroviral therapy (ART). *We report 1 year mortality estimates from a multiregional (eastern Europe, western Europe, and Latin America) prospective cohort study: the TB:HIV study.*

Methods: Consecutive HIV-positive patients aged 16 years or older with a diagnosis of tuberculosis between Jan 1, 2011, and Dec 31, 2013, were enrolled from 62 HIV and tuberculosis clinics in 19 countries in eastern Europe, western Europe, and Latin America. The primary endpoint was death within 12 months after starting tuberculosis treatment; all deaths were classified according to whether or not they were tuberculosis related. Follow-up was either until death, the final visit, or 12 months after baseline, whichever occurred first. *Risk factors for all-cause and tuberculosis-related deaths were assessed* using Kaplan-Meier estimates and Cox models.

Findings: Of 1406 patients (834 in eastern Europe, 317 in western Europe, and 255 in Latin America), 264 (19%) died within 12 months. 188 (71%) of these deaths were tuberculosis related. The probability of all-cause death was 29% (95% CI 26-32) in eastern Europe, 4% (3-7) in western Europe, and 11% (8-16) in Latin America (p<0.0001) and the corresponding probabilities of tuberculosis-related death were 23% (20-26), 1% (0-3), and 4% (2-8), respectively (p<0.0001).
Patients receiving care outside eastern Europe had a 77% decreased risk of death: adjusted hazard ratio (aHR) 0.23 (95% CI 0.16-0.31). In eastern Europe, compared with patients who started a regimen with at least three active antituberculosis drugs, those who started fewer than three active antituberculosis drugs were at a higher risk of tuberculosis-related death (aHR 3.17; 95% CI 1.83-5.49) as were those who did not have baseline drug-susceptibility tests (2.24; 1.31-3.83). Other prognostic factors for increased tuberculosis-related mortality were disseminated tuberculosis and a low CD4 cell count. 18% of patients were receiving ART at tuberculosis diagnosis in eastern Europe compared with 44% in western Europe and 39% in Latin America (p<0.0001); 12 months later the proportions were 67% in eastern Europe, 92% in western Europe, and 85% in Latin America (p<0.0001).

Interpretation: Patients with HIV and tuberculosis in eastern Europe have a risk of death nearly four-times higher than that in patients from western Europe and Latin America. This increased mortality rate is associated with modifiable risk factors such as lack of drug susceptibility testing and suboptimal initial antituberculosis treatment in settings with a high prevalence of drug resistance. Urgent action is needed to improve tuberculosis care for patients living with HIV in eastern Europe.

Abstract access

Editor’s notes: Eastern Europe is experiencing one of the fastest growing HIV epidemics globally. Within this, the number of HIV-positive people with tuberculosis (TB) is also rising rapidly, posing a significant public health challenge. The authors have previously reported retrospective data illustrating 30% mortality at one year among HIV-positive people with TB in eastern Europe. This was noted to be at least three times higher than mortality among people from western Europe and Argentina. Within this study they go further to provide prospective data with comparison across multiple regions. They also highlight prognostic markers associated with death. The study spans across eastern Europe, western Europe and Latin America with a cohort of 1406 people. It robustly demonstrates a significant excess of TB-associated mortality in HIV-positive people with TB receiving care in eastern Europe. The cumulative probability of TB-associated death at 12 months in eastern Europe was 23% (95% confidence interval [CI] 20 – 26), versus 1% (95% CI 0 - 3) in western Europe and 4% (95% CI 2-8) in Latin America. Prognostic markers associated with an increased risk of death included multidrug-resistant TB, disseminated TB and modifiable factors such as choice of initial anti-TB regimen and a lack of baseline drug susceptibility tests. These findings highlight the hugely detrimental impact of the fragmented system of HIV and TB services within eastern Europe. Such inequality in outcomes emphasises the need for urgent strategic change. Co-ordinated care across HIV and TB services, alongside timely and appropriate diagnostics and treatment, is of paramount importance.

Measuring the impact of antiretroviral therapy roll-out on population level fertility in three African countries.


Background: UNAIDS official estimates of national HIV prevalence are based on trends observed in antenatal clinic surveillance, after adjustment for the reduced fertility of HIV positive women. Uptake of ART may impact on the fertility of HIV positive women, implying a need to re-estimate the
adjustment factors used in these calculations. We analyse the effect of antiretroviral therapy (ART) provision on population-level fertility in Southern and East Africa, comparing trends in HIV infected women against the secular trends observed in uninfected women.

Methods: We used fertility data from four community-based demographic and HIV surveillance sites: Kisesa (Tanzania), Masaka and Rakai (Uganda) and uMkhanyakude (South Africa). All births to women aged 15-44 years old were included in the analysis, classified by mother's age and HIV status at time of birth, and ART availability in the community. Calendar time period of data availability relative to ART introduction varied across the sites, from 5 years prior to ART roll-out, to 9 years after. Calendar time was classified according to ART availability, grouped into pre ART, ART introduction (available in at least one health facility serving study site) and ART available (available in all designated health facilities serving study site). We used Poisson regression to calculate age adjusted fertility rate ratios over time by HIV status, and investigated the interaction between ART period and HIV status to ascertain whether trends over time were different for HIV positive and negative women.

Results: Age-adjusted fertility rates declined significantly over time for HIV negative women in all four studies. However HIV positives either had no change in fertility (Masaka, Rakai) or experienced a significant increase over the same period (Kisesa, uMkhanyakude). HIV positive fertility was significantly lower than negative in both the pre ART period (age adjusted fertility rate ratio (FRR) range 0.51 95%CI 0.42-0.61 to 0.73 95%CI 0.64-0.83) and when ART was widely available (FRR range 0.57 95%CI 0.52-0.62 to 0.83 95%CI 0.78-0.87), but the difference has narrowed. The interaction terms describing the difference in trends between HIV positives and negatives are generally significant.

Conclusions: Differences in fertility between HIV positive and HIV negative women are narrowing over time as ART becomes more widely available in these communities. Routine adjustment of ANC data for estimating national HIV prevalence will need to allow for the impact of treatment.

Abstract  Full-text [free] access

Editor’s notes: Antenatal care (ANC) clinics records on demographic characteristics and HIV status of attenders are a major component of primary data used to estimate HIV prevalence in sub-Saharan Africa. Prior to scale-up of antiretroviral therapy (ART), the fertility of women living with HIV was lower than that for people without HIV. This means that prevalence estimates from ANC data were adjusted to avoid underestimating the true population fertility rates.

This paper analyses the changing fertility patterns in four longitudinal community-based cohorts in eastern and southern Africa. The study finds that differences in fertility rates between women living with HIV and women without HIV are narrowing as ART is scaled-up, although substantial differences still exist. There was considerable variation in the patterns between the sites reflecting the differing local epidemic profiles. The authors explain this variation as being due to various factors including biological (increased fertility associated with viral suppression), or behavioural (increased fertility among women experiencing widowhood and then forming new partnerships). The impact of treatment on fertility needs to be incorporated into models of HIV prevalence estimated from ANC data, to inform national policy makers measuring their progress towards HIV elimination targets.

Three months of weekly rifapentine plus isoniazid for treatment of M. tuberculosis infection in HIV co-infected persons.
Objective: Compare the effectiveness, tolerability, and safety of three months of weekly rifapentine plus isoniazid under direct observation (3HP) vs. 9 months of daily isoniazid (9H) in HIV-infected persons.

Design: prospective, randomized, open-label non-inferiority trial.

Setting: U.S., Brazil, Spain, Peru, Canada, and Hong Kong.

Participants: HIV-infected persons who were tuberculin skin test positive or close contacts of tuberculosis cases.

Intervention: 3HP vs. 9H.

Main outcome measures: The effectiveness endpoint was tuberculosis; the non-inferiority margin was 0.75%. The tolerability endpoint was treatment completion; the safety endpoint was drug discontinuation due to adverse drug reaction.

Results: Median baseline CD4+ counts were 495 (IQR: 389-675) and 538 (IQR: 418-729) cells/mm³ in the 3HP and 9H arms, respectively (P = 0.09). In the modified intention to treat analysis, there were two tuberculosis cases among 206 persons (517 person-years (p-y) of follow-up) in the 3HP arm (0.39 per 100 p-y) and six tuberculosis cases among 193 persons (481 p-y of follow-up) in the 9H arm (1.25 per 100 p-y). Cumulative tuberculosis rates were 1.01% vs. 3.50% in the 3HP and 9H arms, respectively (rate difference: -2.49%; upper bound of the 95% confidence interval (CI) of the difference: 0.60%). Treatment completion was higher with 3HP (89%) than 9H (64%) (P < 0.001), and drug discontinuation due to an adverse drug reaction was similar (3% vs. 4%; P = 0.79) in 3HP and 9H, respectively.

Conclusions: Among HIV-infected persons with median CD4+ count of approximately 500 cells/mm³, 3HP was as effective and safe for treatment of latent M. tuberculosis infection as 9H, and better tolerated.

Abstract access

Editor’s notes: People with HIV are at higher risk of reactivation of latent tuberculosis (TB). The standard treatment for latent TB, with six to nine months of daily isoniazid, is effective, but treatment completion rates are typically low, and implementation has been poor. Shorter, effective regimens to treat latent TB are therefore necessary, and rifapentine and isoniazid, given weekly for 12 weeks, is one such candidate regimen. The analysis reported in this paper is a sub-study of a larger trial which was reported in 2011 (Sterling et al, NEJM 2011;365:2155). The main trial was open to people regardless of HIV status, but few HIV-positive people were enrolled. Trial enrolment was therefore continued for HIV-positive people, and this paper reports outcomes among this group.

Although the number of tuberculosis events was very small in this sub-study (two versus six people developed tuberculosis in the rifapentine-isoniazid versus isoniazid only arms), the rifapentine-isoniazid regimen, given directly-observed, was non-inferior to self-administered isoniazid, similar to the results of the main trial. Treatment completion was substantially better with the rifapentine-isoniazid regimen, as expected for a shorter regimen given under direct observation. The rifapentine-isoniazid regimen was equally well-tolerated to the isoniazid-only regimen.
This study provides evidence that rifapentine-isoniazid has potential as an alternative to isoniazid for the treatment of latent tuberculosis among HIV-positive people. Several questions remain. Weekly directly-observed therapy could be difficult to implement in resource-limited settings, especially if people are required to travel to health centres to receive their weekly dose, and the effectiveness of this regimen is uncertain when self-administered. The weekly dose represents a substantial pill burden unless combination tablets are available, and there are potential drug interactions between rifapentine and some antiretroviral agents. Further research is necessary to establish whether, in settings where the risk of tuberculosis re-infection is high, a single 12-week course of rifapentine-isoniazid has a long-lasting effect.