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

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UNAIDS
1. HIV testing and treatment

Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study.


Background: Antiretroviral therapy (ART) is crucial for controlling HIV-1 infection through wide-scale treatment as prevention and pre-exposure prophylaxis (PrEP). Potent tenofovir disoproxil fumarate-containing regimens are increasingly used to treat and prevent HIV, although few data exist for frequency and risk factors of acquired drug resistance in regions hardest hit by the HIV pandemic. We aimed to do a global assessment of drug resistance after virological failure with first-line tenofovir-containing ART.

Methods: The TenoRes collaboration comprises adult HIV treatment cohorts and clinical trials of HIV drug resistance testing in Europe, Latin and North America, sub-Saharan Africa, and Asia. We extracted and harmonised data for patients undergoing genotypic resistance testing after virological failure with a first-line regimen containing tenofovir plus a cytosine analogue (lamivudine or emtricitabine) plus a non-nucleotide reverse-transcriptase inhibitor (NNRTI; efavirenz or nevirapine). We used an individual participant-level meta-analysis and multiple logistic regression to identify covariates associated with drug resistance. Our primary outcome was tenofovir resistance, defined as presence of K65R/N or K70E/G/Q mutations in the reverse transcriptase (RT) gene.

Findings: We included 1926 patients from 36 countries with treatment failure between 1998 and 2015. Prevalence of tenofovir resistance was highest in sub-Saharan Africa (370/654 [57%]). Pre-ART CD4 cell count was the covariate most strongly associated with the development of tenofovir resistance (odds ratio [OR] 1.50, 95% CI 1.27-1.77 for CD4 cell count <100 cells per µL). Use of lamivudine versus emtricitabine increased the risk of tenofovir resistance across regions (OR 1.48, 95% CI 1.20-1.82). Of 700 individuals with tenofovir resistance, 578 (83%) had cytosine analogue resistance (M184V/I mutation), 543 (78%) had major NNRTI resistance, and 457 (65%) had both. The mean plasma viral load at virological failure was similar in individuals with and without tenofovir resistance (145 700 copies per mL [SE 12 480] versus 133 900 copies per mL [SE 16 650; p=0.626]).

Interpretation: We recorded drug resistance in a high proportion of patients after virological failure on a tenofovir-containing first-line regimen across low-income and middle-income regions. Effective surveillance for transmission of drug resistance is crucial.

Abstract Full-text [free] access

Editor’s notes: Global surveillance for tenofovir (TDF) resistance is important at a time of expanding use of TDF-containing regimens for treatment and prevention. This collaborative analysis used data collated from several small studies in different settings. Overall, around one in three people who had failed on TDF-containing treatment had evidence of TDF resistance, although this frequency varied between 20% in Europe to almost 60% in Africa. Mutations associated with NNRTIs and lamivudine/emtricitabine resistance were more common overall and were present in most people with TDF resistance.

The regional variation probably reflects differences in clinical practice and study inclusion criteria. All European studies involved cohorts with frequent viral load monitoring, whereas half of the African
cohorts had no routine viral load monitoring. All European studies included people with virologic failure but with low-level viraemia (viral load <1000 copies/ml) whereas almost all African studies included only people with viral load >1000 copies/ml.

While these data provide useful estimates of the frequency of drug resistance mutations in people with virologic failure on first-line ART, there should be caution about extrapolating beyond this. Reports from cohort studies with an accurate denominator of all people starting TDF-containing first-line ART would be useful to give more reliable estimates of overall incidence of acquired TDF resistance. Moreover, there remains a need for representative population-based surveillance for acquired and transmitted drug resistance. So far, global surveillance has detected limited evidence of transmitted TDF-associated mutations, but this needs to be monitored closely, especially in high incidence settings.

Adverse events associated with abacavir use in HIV-infected children and adolescents: a systematic review and meta-analysis.


Background: Concerns exist about the toxicity of drugs used in the implementation of large-scale antiretroviral programmes, and documentation of antiretroviral toxicity is essential. We did a systematic review and meta-analysis of adverse events among children and adolescents receiving regimens that contain abacavir, a widely used antiretroviral drug.

Methods: We searched bibliographic databases and abstracts from relevant conferences from Jan 1, 2000, to March 1, 2015. All experimental and observational studies of HIV-infected patients aged 0–18 years who used abacavir, were eligible. Incidence of adverse outcomes in patients taking abacavir (number of new events in a period divided by population at risk at the beginning of the study) and relative risks (RR) compared with non-abacavir regimens were pooled with random effects models.

Findings: Of 337 records and 21 conference abstracts identified, nine studies (eight full-text articles and one abstract) collected information about 2546 children, of whom 1769 (69%) were on abacavir regimens. Among children and adolescents taking abacavir, hypersensitivity reactions (eight studies) had a pooled incidence of 2.2% (95% CI 0.4-5.2); treatment switching or discontinuation (seven studies) pooled incidence was 10.9% (2.1-24.3); of grade 3-4 adverse events (six studies) pooled incidence was 9.9% (2.4-20.9); and adverse events other than hypersensitivity reaction (six studies) pooled incidence was 21.5% (2.8-48.4). Between-study inconsistency was significant for all outcomes (p<0.0001 for all inconsistencies). Incidence of death (four studies) was 3.3% (95% CI 1.5-5.6). In the three randomised clinical trials with comparative data, no increased risk of hypersensitivity reaction (pooled RR 1.08; 95% CI 0.19-6.15), grade 3 or 4 events (0.79 [0.44-1.42]), or death (1.72 [0.77-3.82]) was noted for abacavir relative to non-abacavir regimens. None of the reported deaths were related to abacavir.

Interpretation: Abacavir-related toxicity occurs early after ART initiation and is manageable. Abacavir can be safely used for first-line or second-line antiretroviral regimens in children and adolescents, especially in sub-Saharan Africa where HLA B5701 genotype is rare.

Abstract access

Editor’s notes: Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI), available as a paediatric formulation. Abacavir in combination with lamivudine is the preferred NRTI backbone for
children aged three to ten years and for adolescents weighing under 35 kilograms. It is thus part of both first- and second-line antiretroviral therapy (ART) regimens recommended for children by World Health Organization (WHO), American and European guidelines.

In the context of implementation of large-scale ART programmes where abacavir is recommended as the NRTI of choice, understanding its toxicity is crucial. In adults the main concern is the increased risk of hypersensitivity reactions, particularly among people with the HLA B5701 genotype, and of myocardial infarction. Children have specific characteristics that affect both the pharmacokinetic profiles of drugs, and also drug tolerability in the short and the long term. Despite the widespread use of abacavir, there has been no systematic evaluation of the toxicity profile of abacavir in children.

This systematic review of nine studies conducted between 2000 and 2015 demonstrates that there is a low risk of hypersensitivity reactions, especially for children living in sub-Saharan Africa, where 90% of children with HIV live. This is consistent with studies in adults which illustrates that the frequency of the HLAB5701 allele genotype in African populations is low, estimated to be less than two percent.

Other adverse events such as gastrointestinal symptoms and laboratory abnormalities were common. Rates of adverse events should be interpreted with caution as these could depend on factors such as other drugs in the regimen, adherence and so on. Furthermore, data on adverse events were obtained from cohort studies that were not blinded and selection or recall bias cannot be excluded.

Notwithstanding this, most adverse events occurred early after initiation of abacavir, were no more common than with other NRTI regimens, and were manageable. Importantly, there were no deaths associated with abacavir in any of the reported studies. This study supports the use of abacavir as a preferred drug in the NRTI backbone for treatment of children living with HIV.

Concerns about covert HIV testing are associated with delayed presentation in Ethiopian adults with suspected malaria: a cross-sectional study.


Background: Although early diagnosis and prompt treatment is important in preventing mortality from malaria, presentation of symptomatic individuals is often relatively late. One possible contributing factor is that fear of covert human immunodeficiency virus (HIV) testing delays presentation in adults. We aimed to survey the magnitude of such concerns and their association with delayed presentation with suspected malaria.

Methods: The study design was a health facility-based cross-sectional survey. The study population consisted of adults with suspected malaria who presented to health centres in central Ethiopia. Data were collected on attitudes to HIV testing and the duration between onset of symptoms and treatment seeking for suspected malaria.

Results: Eight hundred and ten individuals provided data. Of these, 406 (50 %) perceived that HIV testing was routinely done on blood donated for malaria diagnosis, and 327 (40 %) considered that community members delayed seeking medical advice because of these concerns. Concerns about HIV testing were associated with delays in attending for malaria diagnosis and treatment, with 117 individuals (29 %) of those with concerns about covert HIV testing waiting for 4 days or more, compared to 89 (22 %) of those who did not have any such concerns (p = 0.03). One hundred and twenty nine (16 %) individuals stated that concern about HIV testing was the main reason for the delay in seeking treatment, and 46 % of these individuals presented after experiencing symptoms of malaria infection for three days or more compared to 22 % of the 681 individuals who had no such concerns (p < 0.001). Analysis stratified by health centre demonstrated
that these associations were a consequence of Meki health centre (odds ratio for duration of symptoms greater than 3 days if patient has concerns about HIV testing was 8.72; 95% confidence intervals 3.63 to 20.97).

Conclusions: In adults living in central Ethiopia, the perception that HIV testing accompanied the investigation of suspected malaria was common. This is likely to impede presentation for early medical treatment in some areas and represents a reversible risk factor that deserves further study.

Abstract Full-text [free] access

Editor’s notes: This study addresses a relatively under-studied issue of concerns about HIV testing among adults with malaria. Previously, the authors of this paper found that about half of guardians of children with malaria symptoms in central Ethiopia thought the children’s blood samples were tested for HIV without consent. Guardians who believed this were more likely to delay bringing children for treatment. In this paper, the authors illustrate that the same is true for adults. In a representative survey of adults presenting with malaria symptoms at five health centres, about half of participants were concerned that their blood sample was secretly tested for HIV without their consent and about one in three thought that many or almost all members of their community believed this. Concern about covert HIV testing was associated with delayed presentation for management of suspected malaria overall, although this was largely due to the issue in one specific health centre. Electricity in the home, better education and urban versus rural home were not associated with this belief, although people in rural areas were more likely to delay treatment-seeking.

Beliefs about health care are culturally specific, so the results may not be generalizable to other contexts, but the belief that blood taken at health centres is secretly tested for HIV has been found in different cultural settings. Prompt treatment for suspected malaria is key and strategies to address these concerns are necessary. Possible strategies include investigations to clarify whether, in fact, blood is being tested for HIV without fully informed consent, and improved confidentiality of blood test results.

2. Elimination of childhood infections

Why did I stop? Barriers and facilitators to uptake and adherence to ART in option B+ HIV care in Lilongwe, Malawi.


Causes for loss-to-follow-up, including early refusals of and stopping antiretroviral therapy (ART), in Malawi's Option B+ program are poorly understood. This study examines the main barriers and facilitators to uptake and adherence to ART under Option B+. In depth interviews were conducted with HIV-infected women who were pregnant or postpartum in Lilongwe, Malawi (N = 65). Study participants included women who refused ART initiation (N = 10), initiated ART and then stopped (N = 26), and those who initiated ART and remained on treatment (N = 29). The barriers to ART initiation were varied and included concerns about partner support, feeling healthy, and needing time to think. The main reasons for stopping ART included side effects and lack of partner support. A substantial number of women started ART after initially refusing or stopping ART. There were several facilitators for re-starting ART, including encouragement from community health workers, side effects subsiding, decline in health, change in partner, and fear of future sickness. Amongst those who remained on ART, desire to prevent transmission and improve
health were the most influential facilitators. Reasons for refusing and stopping ART were varied. ART-related side effects and feeling healthy were common barriers to ART initiation and adherence. Providing consistent pre-ART counseling, early support for patients experiencing side effects, and targeted efforts to bring women who stop treatment back into care may improve long term health outcomes.

Abstract Full-text [free] access

Editor’s notes: Option B+ is a policy recommendation of World Health Organisation (WHO) that offers all pregnant and breast-feeding women living with HIV, life-long antiretroviral therapy (ART), regardless of CD4 count or clinical stage. Few studies have examined the challenges faced by pregnant and breast-feeding women, as they navigate the prevention of mother-to-child transmission cascade. The objective of this study was to identify the main barriers and facilitators to uptake and adherence to ART under Option B+ in Lilongwe, Malawi. This was done by conducting qualitative interviews (n=65) with women living with HIV who were pregnant or post-partum and had initiated ART, and women who refused or had stopped treatment.

The most important facilitator for initially starting and remaining on ART was the need to prevent transmission to their infants and to maintain health (prevent illness). Furthermore, ART was viewed as a solution to women’s health issues. This was especially the case when women believed that their health problems were associated with their HIV infection. There were a number of reasons that emerged for refusing ART. For most women the urgency of having to initiate ART under Option B+ was a major challenge. Women felt that they needed time, either to discuss their status with their partner or to accept their own status. In particular, the desire to speak to their partners emerged quite prominently reflecting a fear of disclosure and concern about their partner’s reaction. Another reason was generally feeling healthy before initiating treatment. Women wanted to wait until their health declined before initiating treatment. Religious beliefs did not play a significant role for most women. Only one woman refused because she believed that God, not healthcare providers, would tell her when she needed to start treatment. Side effects were the most commonly reported reason for stopping ART. Half of the 26 (N = 13) respondents who stopped ART did so because they experienced side effects, which included dizziness, nausea or vomiting, nightmares and hallucinations (9%). Women who had side effects also expressed challenges with food security. Side effects made some women question the efficacy of ART. The lack of partner support was another important barrier to ART adherence as women reported fear of disclosing their status to their husbands. Interestingly, although partner support was factored into women’s decision making, in most cases it was not the main consideration. The majority of partners (n=44) accepted their wives’ status, often sending reminders to take ART every night. However, many women did not return to the clinic even though their partners accepted their status (N = 17). One woman, for instance, took the money her husband gave her for transport to the clinic and spent it on other things. Forgetting to take pills or losing pills were other reasons given for lack of adherence. Stigma within the community was acknowledged as an issue, but there were few reports of overt discrimination. Further, even though some women refused or stopped ART, many of them re-started for reasons such as, feeling encouraged by a community health worker (CHW) or someone like a CHW. This was through their monthly home visits to check on women’s use of ART and to provide treatment support such as explaining the side-effects, counselling husbands and encouraging women to re-start. Decline in health, fear of future sickness, as well as reduction in side-effects were mentioned as reasons for re-starting on ART.

Overall, study authors mention that in the context of Option B+, inadequate time in preparing to initiate ART, as well as side effects emerged as more significant barriers as compared to previous studies on barriers and facilitators in non-Option B+ contexts. Economic barriers to care did not emerge as very
significant in this study when compared to other studies; however, a lack of food affects the severity of side effects. This suggests that economic barriers may manifest as an indirect mechanism that affects ART use. A strength of this study is the use of in-depth interviews with a range of women; not just women who stayed on ART, but also women who refused, stopped and re-started in the context of Option B+. Even though there might be overlap between the findings here and other qualitative research, particular barriers become more salient for women initiating ART in the context of Option B+. In prior assessments, women were only initiated on ART after being immunologically compromised, an assessment which often took longer than a month. This gave women time to reflect and accept their condition and communicate with their partner. In the case of Option B+ women felt they needed this time to prepare. The study demonstrates that challenges with uptake and adherence to ART remain. More time and support for women in decision-making, consistent pre-ART counselling, and support with side-effects may contribute to improvements in the long-run. As ART becomes increasingly normalised, some of these barriers may disappear.

Conditional cash transfers and uptake of and retention in prevention of mother-to-child HIV transmission care: a randomised controlled trial.


Background: Novel strategies are needed to increase retention in and uptake of prevention of mother-to-child HIV transmission (PMTCT) services in sub-Saharan Africa. We aimed to determine whether small, increasing cash payments, which were conditional on attendance at scheduled clinic visits and receipt of proposed services can increase the proportions of HIV-infected pregnant women who accept available PMTCT services and remain in care.

Methods: In this randomised controlled trial, we recruited newly diagnosed HIV-infected women, who were 32 or less weeks pregnant, from 89 antenatal care clinics in Kinshasa, Democratic Republic of Congo, and randomly assigned (1:1) them to either the intervention group or the control group using computer-based randomisation with varying block sizes of four, six, and eight. The intervention group received compensation on the condition that they attended scheduled clinic visits and accepted offered PMTCT services (US$5, plus US$1 increment at every subsequent visit), whereas the control group received usual care. Outcomes assessed included retention in care at 6 weeks’ post partum and uptake of PMTCT services, measured by attendance of all scheduled clinic visits and acceptance of proposed services up to 6 weeks’ post partum. Analyses were by intention to treat. This trial is registered with ClinicalTrials.org, number NCT01838005.

Findings: Between April 18, 2013, and Aug 30, 2014, 612 potential participants were identified, 545 were screened, and 433 were enrolled and randomly assigned; 217 to the control group and 216 to the intervention group. At 6 weeks’ post partum, 174 participants in the intervention group (81%) and 157 in the control group (72%) were retained in care (risk ratio [RR] 1.11; 95% CI 1.00-1.24). 146 participants in the intervention group (68%) and 116 in the control group (54%) attended all clinic visits and accepted proposed services (RR 1.26; 95% CI 1.08-1.48). Results were similar after adjustment for marital status, age, and education.

Interpretation: Among women with newly diagnosed HIV, small, incremental cash incentives resulted in increased retention along the PMTCT cascade and uptake of available services. The cost-effectiveness of these incentives and their effect on HIV-free survival warrant further investigation.
Abstract access

Editor’s notes: Eliminating new HIV infections in children and keeping their mothers alive is a crucial component in ending the AIDS epidemic. However, engaging and retaining women in prevention of mother-to-child transmission services can be problematic, with high rates of loss to follow up being documented in many sub-Saharan countries. Noting the success of financial incentives to promote positive health behaviours, this study applies this approach in antenatal care clinics in Kinshasa, Democratic Republic of Congo.

Newly-diagnosed HIV-positive pregnant women were randomised to receive usual care versus small escalating cash payments. This payment started at $5, increasing by $1 each visit, on the proviso they attended scheduled appointments and adhered to medical advice until six weeks post-partum. This cash offer resulted in both increased attendance to all visits and increased retention at six weeks post-partum. As might be expected, the effect was strongest among the most vulnerable women, including women who walked to the clinic. This is in line with the rationale that addressing non-medical, structural barriers enables engagement with care.

It is worth noting that follow-up stopped at six weeks post-partum so the impact of the programme over a longer period needs further exploration. However, the study is reported to be the first of its kind in prevention of mother-to-child transmission of HIV and certainly supports the need for continued research into the use of financial incentives for prevention of mother-to-child transmission.

3. Combination prevention

Use of a vaginal ring containing dapivirine for HIV-1 prevention in women.


Background: Antiretroviral medications that are used as prophylaxis can prevent acquisition of human immunodeficiency virus type 1 (HIV-1) infection. However, in clinical trials among African women, the incidence of HIV-1 infection was not reduced, probably because of low adherence. Longer-acting methods of drug delivery, such as vaginal rings, may simplify use of antiretroviral medications and provide HIV-1 protection.

Methods: We conducted a phase 3, randomized, double-blind, placebo-controlled trial of a monthly vaginal ring containing dapivirine, a non-nucleoside HIV-1 reverse-transcriptase inhibitor, involving women between the ages of 18 and 45 years in Malawi, South Africa, Uganda, and Zimbabwe.

Results: Among the 2629 women who were enrolled, 168 HIV-1 infections occurred: 71 in the dapivirine group and 97 in the placebo group (incidence, 3.3 and 4.5 per 100 person-years, respectively). The incidence of HIV-1 infection in the dapivirine group was lower by 27% (95% confidence interval [CI], 1 to 46; P=0.05) than that in the placebo group. In an analysis that excluded data from two sites that had reduced rates of retention and adherence, the incidence of HIV-1
infection in the dapivirine group was lower by 37% (95% CI, 12 to 56; P=0.007) than that in the placebo group. In a post hoc analysis, higher rates of HIV-1 protection were observed among women over the age of 21 years (56%; 95% CI, 31 to 71; P<0.001) but not among those 21 years of age or younger (-27%; 95% CI, -133 to 31; P=0.45), a difference that was correlated with reduced adherence. The rates of adverse medical events and antiretroviral resistance among women who acquired HIV-1 infection were similar in the two groups.

Conclusions: A monthly vaginal ring containing dapivirine reduced the risk of HIV-1 infection among African women, with increased efficacy in subgroups with evidence of increased adherence.

Abstract

Editor's notes: Women bear a larger proportion of the HIV burden worldwide due to biological and behavioural factors. As a result, the HIV prevention field has focused research over the past couple of decades to identify new prevention options especially for women, to reduce this burden. The study presented in this paper is the first to publish phase III efficacy trial results for a vaginal ring containing the antiretroviral drug dapivirine for HIV prevention. The ring is designed to prevent HIV acquisition locally within the vagina in HIV negative women and kept in the body for a period of four weeks. This strategy is meant to address two components of adherence and side effects. A longer-acting product and local application is contrasted with the daily and systemic use of oral pre-exposure prophylaxis, a regimen which can be difficult to maintain. This study found that the dapivirine ring did not protect women with a high rate of efficacy, 27% overall. Interestingly, the sub-analyses of the data illustrated that there was better protection in women with better adherence, and in women who were over the age of 21. Further explorations of the data along with the qualitative findings from the study will surely provide more valuable insights into the low overall rate of efficacy, and perhaps most importantly into why age made such a difference in rates of protection. As mentioned in the paper, a second study on the ring, which was presented at CROI 2016, publishing similar results, and those results combined with the data from this study will further our knowledge regarding the viability of this HIV prevention option.

I knew I would be safer. Experiences of Kenyan HIV serodiscordant couples soon after pre-exposure prophylaxis (PrEP) initiation.


Pre-exposure prophylaxis (PrEP) for HIV-uninfected persons is highly efficacious for HIV prevention. Understanding how people at risk for HIV will use PrEP is important to inform PrEP scale-up and implementation. We used qualitative methods to gather insights into couples’ early experiences with PrEP use within the Partners Demonstration Project, an open-label implementation study evaluating integrated delivery of PrEP and antiretroviral therapy (ART). PrEP is offered to HIV uninfected partners until the HIV-infected partner initiates and sustains ART use (i.e., PrEP as a “bridge” to ART initiation and viral suppression). From August 2013 to March 2014 we conducted 20 in-depth dyadic interviews (n = 40) with heterosexual HIV serodiscordant couples participating at the Thika, Kenya study site, exploring how couples make decisions about using PrEP for HIV prevention. We developed and applied deductive and inductive codes to identify key themes related to experiences of PrEP initiation and use of time-limited PrEP. Couples reported that PrEP offered them an additional strategy to reduce the risk of HIV transmission, meet their fertility desires, and cope with HIV serodiscordance. Remaining HIV
negative at follow-up visits reinforced couples’ decisions and motivated continued adherence to PrEP. In addition, confidence in their provider’s advice and client-friendly services were critical to their decisions to initiate and continue use of PrEP. **Strategies for wide-scale PrEP delivery for HIV serodiscordant couples in low resource settings may include building capacity of health providers to counsel on PrEP adoption while addressing couples’ concerns and barriers to adoption and continued use.**

Abstract access

**Editor’s notes:** This paper is based on findings from the Partners Demonstration Project. This project evaluated the implementation of ART and PrEP for HIV-1 prevention in African heterosexual HIV-1 serodiscordant couples in Uganda and Kenya. As has been reported elsewhere, the research achieved impressive reductions in HIV-incidence. The strategy adopted in the project was to provide PrEP to the HIV-negative partner until the HIV-positive partner had sustained their use of ART for six months. Using data from Kenya, the authors describe in this paper the value placed by couples on PrEP, which underpinned the study success. Couples wanted to use PrEP because PrEP (and ART) provided the possibility of reduced HIV transmission. In addition to the findings on reasons for PrEP use, this paper also offers insights into couple dynamics. The research was conducted with mutually disclosed HIV serodiscordant couples. The authors illustrated through their analysis and the excerpts from interviews used in the text, the importance of communication between partners. They also, importantly, illustrate differences between couples. The authors describe the use of both verbal and non-verbal communication in discussions about PrEP and ART. Through the data in this paper a picture is built up on the importance of open and frank communication in decisions about using and sustaining the use of PrEP and ART. In a study setting, couples could be afforded support which might be scarce in public health settings. Even so, the findings underline the value of being sensitive to context and individual needs, in supporting PrEP and ART roll-out.

**Psychological and behavioral interventions to reduce HIV risk: evidence from a randomized control trial among orphaned and vulnerable adolescents in South Africa.**


Evidence-based approaches are needed to address the high levels of sexual risk behavior and associated HIV infection among orphaned and vulnerable adolescents. **This study recruited adolescents from a support program for HIV-affected families and randomly assigned them by cluster to receive one of the following: (1) a structured group-based behavioral health intervention; (2) interpersonal psychotherapy group sessions; (3) both interventions; or (4) no new interventions.** With 95% retention, 1014 adolescents were interviewed three times over a 22-month period. Intent-to-treat analyses, applying multivariate difference-in-difference probit regressions, were performed separately for boys and girls to assess intervention impacts on sexual risk behaviors. Exposure to a single intervention did not impact behaviors. Exposure to both interventions was associated with risk-reduction behaviors, but the outcomes varied by gender: boys reported fewer risky sexual partnerships (beta = -.48, p = .05) and girls reported more consistent condom (beta = 1.37, p = .02). There was no difference in the likelihood of sexual debut for either gender. Providing both psychological and behavioral interventions resulted in long-term changes in sexual behavior that were not present when either intervention was provided in isolation. Multifaceted approaches for reducing sexual risk behaviors among vulnerable adolescents hold significant promise for mitigating the HIV epidemic among this priority population.
Abstract access

Editor’s notes: HIV infection is the leading cause of mortality among adolescents in sub-Saharan Africa and this age group is a priority group for programmes. Within this age-group, orphaned adolescents are particularly vulnerable, and a major risk factor for HIV infection in this population is psychological distress, which is a key factor in sexual decision-making. This study suggests that a multifaceted approach that addresses both psychological well-being and sexual risk-taking behaviour may reduce risky sexual behaviour. Such activities are more likely to be successful if other more basic needs, such as economic security, are already being met. However, the strength of the findings is limited by the reliance on self-reported behaviours rather than biological endpoints. The authors highlight a number of issues that could improve the efficacy of programmes, including introducing gender-specific sessions and activities and supplemental school-based programmes.

4. Key populations

A systematic review of HIV risk behaviors and trauma among forced and unforced migrant populations from low and middle-income countries: state of the literature and future directions.


The aim of the current systematic review is to examine the relationship between trauma and HIV risk behaviors among both forced and unforced migrant populations from low and middle-income countries (LMIC). We conducted a review of studies published from 1995 to 2014. Data were extracted related to (1) the relationship between trauma and HIV risk behaviors, (2) methodological approach, (3) assessment methods, and (4) differences noted between forced and unforced migrants. A total of 340 records were retrieved with 24 studies meeting inclusion criteria. Our review demonstrated an overall relationship between trauma and HIV risk behaviors among migrant populations in LMIC, specifically with sexual violence and sexual risk behavior. However, findings from 10 studies were not in full support of the relationship. Findings from the review suggest that additional research using more rigorous methods is critically needed to understand the nature of the relationship experienced by this key-affected population.

Abstract access

Editor’s notes: The number of forced and unforced migrants is growing globally. Refugees, asylum seekers, and internally displaced persons (IDP) are forced migrants who often migrate due to political violence or conflict. Labour migrants are seen as unforced migrants who choose to emigrate for economic reasons. About half of labour migrants worldwide are women who are increasingly migrating on their own being the sole income provider for their families. With respect to trauma exposure and HIV risk in settings of long-term political violence and conflict, the distinction between war migrant, non-war migrant, and long-term resident is blurred. This in-depth review of 24 studies related to low-and middle-income countries (LMIC), mostly from sub-Saharan Africa, found findings similar to those from non-migrant populations in high-income countries. These linked traumatic experiences among migrant populations with HIV risk behaviours. Sexual violence was consistently associated with HIV sexual risk behaviours and HIV infection across the studies. But there are big gaps in the scientific literature. For example, the relationship between trauma and HIV risks has been explored for female labour migrants who are sex workers but not among women who have other
occupations. Most studies addressed sexual risk and alcohol dependence, but injecting drug risk behaviors and use of any illicit drugs were virtually ignored by most studies. Few studies examined a possible link for trauma that occurred pre-migration and post-migration. Three qualitative studies examined male migrants who have sex with men, finding that violent experiences and discrimination and stigma associated with homophobia, combined with other migrant-associated traumas, can compound their mental health outcomes and subsequent HIV risk behaviors – but all were only conducted in the last four years. No studies were found that focused on HIV prevention programmes to address trauma and HIV risks among migrant workers in LMIC. However, the studies do reveal important factors that prevention programmes would have to consider. For example, concerns among labour migrants about dangerous working conditions may take precedence over HIV risk perceptions and the need for safer sex. This systematic review presents a wealth of information while highlighting the need to improve the quality of scientific research examining the link between HIV and trauma among both forced and unforced migrants in LMIC.

Cost-effectiveness of combined sexual and injection risk reduction interventions among female sex workers who inject drugs in two very distinct Mexican border cities.


Background: We evaluated the cost-effectiveness of combined single session brief behavioral intervention, either didactic or interactive (Mujer Mas Segura, MMS) to promote safer-sex and safer-injection practices among female sex workers who inject drugs (FSW-IDUs) in Tijuana (TJ) and Ciudad-Juarez (CJ) Mexico. Data for this analysis was obtained from a factorial RCT in 2008-2010 coinciding with expansion of needle exchange programs (NEP) in TJ, but not in CJ.

Methods: A Markov model was developed to estimate the incremental cost per quality adjusted life year gained (QALY) over a lifetime time frame among a hypothetical cohort of 1000 FSW-IDUs comparing a less intensive didactic vs. a more intensive interactive format of the MMS, separately for safer sex and safer injection combined behavioral interventions. The cost for antiretroviral therapy was not included in the model. We applied a societal perspective, a discount rate of 3% per year and currency adjusted to US$2014. A multivariate sensitivity analysis was performed. The combined and individual components of the MMS interactive behavioral intervention were compared with the didactic formats by calculating the incremental cost-effectiveness ratios (ICER), defined as incremental unit of cost per additional health benefit (e.g., HIV/STI cases averted, QALYs) compared to the next least costly strategy. Following guidelines from the World Health Organization, a combined strategy was considered highly cost-effective if the incremental cost per QALY gained fell below the gross domestic product per capita (GDP) in Mexico (equivalent to US$10 300).

Findings: For CJ, the mixed intervention approach of interactive safer sex/didactic safer injection had an incremental cost-effectiveness ratio (ICER) of US$4360 ($310-$7200) per QALY gained compared with a dually didactic strategy. Using the dually interactive strategy had an ICER of US$5874 ($310-$7200) compared with the mixed approach. For TJ, the combination of interactive safer sex/didactic safer injection had an ICER of US$5921 ($104-$9500) per QALY compared with dually didactic. Strategies using the interactive safe injection intervention were dominated due to lack of efficacy advantage. The multivariate sensitivity analysis showed a 95% certainty that in both CJ and TJ the ICER for the mixed approach (interactive safer sex didactic safer injection intervention) was less than the GDP per capita for Mexico. The dual interactive approach met this threshold consistently in CJ, but not in TJ.
Interpretation: In the absence of an expanded NEP in CJ, the combined-interactive formats of the MMS behaviorial intervention is highly cost-effective. In contrast, in TJ where NEP expansion suggests that improved access to sterile syringes significantly reduced injection-related risks, the interactive safer-sex combined didactic safer-injection was highly cost-effective compared with the combined didactic versions of the safer-sex and safer-injection formats of the MMS, with no added benefit from the interactive safer-injection component.

Abstract

Editor’s notes: Female sex workers who inject drugs are a particularly vulnerable group with potential risks of HIV infection stemming from both condomless sex and use of contaminated injecting equipment. In the northern border towns of Mexico, which are on major drug trafficking routes into the United States, the prevalence of HIV among female sex workers who inject drugs is 12%. This is in comparison with 6% among female sex workers who do not inject drugs and 0.3% among the general population. In this context, the authors conducted a cost-effectiveness analysis of a combined single-session brief behavioral programme. It was either didactic or interactive, to promote safer sexual and injection practices among female sex workers who inject drugs in two Mexican cities: Ciudad Juarez and Tijuana.

The authors found that the programme can be highly cost-effective in reducing HIV risky behaviours, although with varying results. Sensitivity analyses suggested that in both cities, the mixed approach (interactive safer sex/didactic safer injection intervention) was highly cost-effective. The dual interactive approach was highly cost-effective in Ciudad Juarez but not in Tijuana.

This article illustrates the importance of targeting programmes that take into consideration city-level contexts. Although the cities are similar in many ways, the double interactive approach was not highly cost-effective in the Tijuana setting. This is likely to be due to the fact that needle syringe distribution at the community level expanded at the same time, making the interactive safer injection practice component redundant. This supports previous research that community-level programmes, such as needle-exchange programmes, could be potentially more cost-effective than individual-level activities. Individual-level activities may then be best suited for settings where needle-syringe programmes are not available, such as in prisons.

Krokodile Injectors in Ukraine: fueling the HIV Epidemic?


This study was designed to assess the characteristics of krokodile injectors, a recent phenomenon in Ukraine, and HIV-related risk factors among people who inject drugs (PWID). In three Ukraine cities, Odessa, Donetsk and Nikolayev, 550 PWID were recruited between December 2012 and October 2013 using modified targeted sampling methods. The sample averaged 31 years of age and they had been injecting for over 12 years. Overall, 39% tested positive for HIV, including 45% of krokodile injectors. In the past 30 days, 25% reported injecting krokodile. Those who injected krokodile injected more frequently (p < 0.001) and they injected more often with others (p = 0.005). Despite knowing their HIV status to be positive, krokodile users did not reduce their injection frequency, indeed, they injected as much as 85% (p = 0.016) more frequently than those who did not know their HIV status or thought they were negative. This behavior was not seen in non-krokodile using PWID. Although only a small sample of knowledgeable HIV positive krokodile users was available (N = 12), this suggests that krokodile users may disregard their HIV status more so than non-krokodile users. In spite of widespread knowledge of its harmful physical consequences, a
growing number of PWID are turning to injecting krokodile in Ukraine. Given the recency of krokodile use in the country, the associated higher frequency of injecting, a propensity to inject more often with others, and what could be a unique level of disregard of HIV among krokodile users, HIV incidence could increase in future years.

Abstract access

**Editor’s notes:** This is an important study among a highly vulnerable population of people who inject drugs where HIV prevalence has been consistently high over the last decade. This is one of the first empirical studies to examine the role of krokodile use on HIV risk acquisition. Krokodile is a home produced drug that has become more popular among people who inject drugs in Ukraine and the Russian Federation over the last five years. There is a long history of injection with home-produced opioids and amphetamines in these countries. The key component of krokodile is codeine, an opioid, but severe side effects have been associated with its injection including tissue damage, gangrene and organ failure. This study highlights some of the characteristics and HIV risk behaviors associated with krokodile injection to inform appropriate HIV prevention programming. Findings note that people who inject krokodile are more likely to inject with others. This reflects the home-produced nature of the drug that facilitates more group injecting as people congregate at places where it is produced to buy and inject. Programmes need to focus on strategies to avoid injecting with other people’s used injecting equipment, such as marking equipment, as can happen in group injecting scenarios. This programme would ensure there are sufficient numbers of clean needles/syringes in circulation. Worryingly, a higher prevalence of HIV was observed among people who inject krokodile, most likely associated with their older age and more frequent injecting. Targeted harm reduction information is urgently needed for krokodile users to prevent further HIV transmission and prevent soft tissue damage. There is already a large network of needle-syringe programmes and opioid substitution therapy available for people who inject drugs in Ukraine. However, access is often reduced since people who inject drugs are concerned about being arrested. Registration as a person who injects drugs causes problems with employment, families and police. Collaboration with the police is necessary to increase access to opioid substitution and needle and syringe programmes. Programmes are also required to reduce the stigma associated with injection in order to address the health needs of this population.

Uptake of PrEP and condom and sexual risk behavior among MSM during the ANRS IPERGAY trial.


The double-blind phase of the randomized ANRS IPERGAY trial, evaluating sexual activity-based oral HIV pre-exposure prophylaxis (PrEP), was conducted among high-risk men who have sex with men (MSM). Results showed an 86% (95% CI: 40-98) relative reduction in HIV incidence among participants with tenofovir disoproxil fumarate-emtricitabine vs. placebo. The present pooled analysis aimed to analyze (i) participants’ adherence to the prescribed treatment and/or condom use during sexual intercourse and (ii) sexual behavior during the double-blind phase of the study. Four hundred MSM were enrolled in the trial. Every 2 months they completed online questionnaires collecting sexual behavior and PrEP adherence data regarding their most recent sexual intercourse. A total of 2232 questionnaires (M0-M24) were analyzed. Changes over time were evaluated using a mixed model accounting for multiple measures. Irrespective of sexual partner and
practice type, on average, 42.6% (min: 32.1-max: 45.8%) reported PrEP use only during their most recent episode of sexual intercourse; 29% (22.9-35.6%) reported both PrEP and condom use; 11.7% (7.2-18.9%) reported condom-use only, and 16.7% (10.8-29.6%) reported no PrEP or condom use with no significant change during the study. Scheduled (i.e., correct) PrEP use was reported on average by 59.0% (47.2-68.5%) of those reporting PrEP use during their most recent sexual intercourse. Overall, 70.3% (65.3-79.4%) and 69.3% (58.3-75.4%) of participants reported, respectively, condomless anal and condomless receptive anal intercourse during their most recent sexual encounter without significant change during follow-up. Overall, on average 83.3% (min: 70.4-max: 89.2%) of participants protected themselves by PrEP intake or condom use or both during the trial, and no increase in at-risk sexual practices was observed. None of these indicators showed significant trend during the follow-up, although we found a tendency toward decrease (p = .19) of the median number of sexual partners strengthening the absence of behavioral disinhibition. On-demand PrEP within a comprehensive HIV prevention package could improve prevention in MSM.

Abstract access

Editor’s notes: HIV pre-exposure prophylaxis (PrEP) is an effective method of HIV prevention, and it is now recognised as a key element of combination prevention strategies in key populations. The IPERGAY trial evaluated the intermittent use of oral PrEP, timed around sexual activity, in gay men and other men who have sex with men. The investigators hypothesised that taking PrEP ‘on demand’, i.e. at the time of sexual activity rather than daily, would improve adherence and therefore its effectiveness. The reduction in HIV incidence in the trial is one of the highest reported at 86%.

This analysis of trial participants in the double-blind phase of the trial demonstrated that PrEP and/or condom use at the most recent sexual intercourse was reported at 80% of visits, and there was no evidence of a change over time. Adherence remained quite high over the 24 months of follow-up, with 60% reporting correct use of PrEP at each visit, although numbers were small owing to early stopping of the placebo arm. As with other studies of PrEP, there was no evidence of an increase in reported sexual risk behaviours over time. In addition, there was some suggestion of a trend towards a decreased number of partners. However, as trial participants were offered a comprehensive care package (including regular adherence and risk reduction counselling), it is difficult to separate the effects of the intensive support from the effects of the PrEP regimen itself.

The successful integration of PrEP into HIV combination prevention programmes will require an understanding of factors that facilitate its uptake and who is most likely to benefit from its use, as well as ensuring regular HIV testing and adequate support services are available.

5. Elimination of gender inequalities


Introduction: Power imbalances within sexual relationships have significant implications for HIV prevention in sub-Saharan Africa. Little is known about how power influences the quality of a
relationship, which could be an important pathway leading to healthy behavior around HIV/AIDS.

Methods: This paper uses data from 448 heterosexual couples (896 individuals) in rural KwaZulu-Natal, South Africa who completed baseline surveys from 2012 to 2014 as part of a couples-based HIV intervention trial. Using an actor-partner interdependence perspective, we assessed: (1) how both partners’ perceptions of power influences their own (i.e., actor effect) and their partner’s reports of relationship quality (i.e., partner effect); and (2) whether these associations differed by gender. We examined three constructs related to power (female power, male equitable gender norms, and shared power) and four domains of relationship quality (intimacy, trust, mutually constructive communication, and conflict).

Results: For actor effects, shared power was strongly and consistently associated with higher relationship quality across all four domains. The effect of shared power on trust, mutually constructive communication, and conflict were stronger for men than women. The findings for female power and male equitable gender norms were more mixed. Female power was positively associated with women’s reports of trust and mutually constructive communication, but negatively associated with intimacy. Male equitable gender norms were positively associated with men’s reports of mutually constructive communication. For partner effects, male equitable gender norms were positively associated with women’s reports of intimacy and negatively associated with women’s reports of conflict.

Conclusions: Research and health interventions aiming to improving HIV-related behaviors should consider sources of shared power within couples and potential leverage points for empowerment at the couple level. Efforts solely focused on empowering women should also take the dyadic environment and men’s perspectives into account to ensure positive relationship outcomes.

Abstract Full-text [free] access

Editor’s notes: This paper reports findings of a study conducted in rural KwaZulu-Natal province in South Africa. KwaZulu-Natal has the highest adult HIV prevalence in South Africa of 17%. The study draws on data from 448 couples (896 individuals) that completed a 2012 baseline study of “Uthando Lwethu” – a randomised controlled trial of a couples-based programme to improve relationship dynamics and uptake of couples-based HIV testing and counselling.

The findings highlight several implications for HIV programmes in sub-Saharan Africa. They illustrate that gender transformative activities may have a positive effect on relationships, especially where they do not inadvertently conflict with relationship values such as intimacy. The findings also highlight the synergistic potential of gender-focused programmes and couple-based programmes focusing on HIV, to both improve relationships and reduce HIV-associated behavioural risk. Further, the findings suggest the importance of the construct of shared gender power when considering the prioritisation of resources and efforts for couple-based programmes. This highlights the potential for developing new ways of conceptualising power with couples that go beyond dyadic constructs at the individual level.

Gender-specific jealousy and infidelity norms as sources of sexual health risk and violence among young coupled Nicaraguans.

Gender inequity negatively affects health in Central America. In 2011, we conducted 60 semistructured interviews and 12 photovoice focus groups with young coupled men and women in Leon, Nicaragua, to explore the ways in which social norms around marriage and gender affect sexual health and gender-based violence. Participants' depictions of their experiences revealed gendered norms around infidelity that provided a narrative to justify male expressions of jealousy, which included limiting partner autonomy, sexual coercion, and physical violence against women, and resulted in increased women's risk of sexually transmitted infections, including HIV. By understanding and taking account of these different narratives and normalized beliefs in developing health- and gender-based-violence interventions, such programs might be more effective in promoting gender-equitable attitudes and behaviors among young men and women in Nicaragua.

Abstract access

Editor's notes: This paper explored persistent gender inequity in Nicaragua and its effects on sexual health and experiences of gender-based violence. The authors draw on an understanding that in Nicaragua gender inequity is expressed through local ideas of 'machismo', the masculine expectation of dominance over women. This is demonstrated through overemphasized heterosexuality, and aggression, and 'marianismo', the feminine expectation of submissiveness, dependence, and sexual naivety. The authors conducted two semi-structured in-depth interviews with 30 young coupled men (n = 15) and women (n = 15) and focus groups with a subsample of women (n = 6) and men (n = 5) who participated in interviews. They also asked these participants to take three photos about a discussion topic, which were discussed at a following session.

Their findings revealed two themes concerning fidelity and jealousy. Participants discussed the social acceptability of infidelity by men, and jealous behaviour by men. Women reported having little power to influence their husbands to remain faithful or to stop being jealous. The authors argue that infidelity and jealousy norms are expressions of gender inequity and impact on women's risk of sexually transmitted infections, sexual coercion, and violence. These factors reflect constrained female sexuality and economic power. The authors conclude that while gender norms in Nicaragua are changing, progress toward gender equity is slow. Programmes to address gender inequity should frame this in terms of jealousy and infidelity, complemented with structural and systemic programmes to address gender-based social and economic inequities.

6. Health systems and services

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis.


Background: Cryptococcal meningitis associated with human immunodeficiency virus (HIV) infection causes more than 600 000 deaths each year worldwide. Treatment has changed little in 20 years, and there are no imminent new anticryptococcal agents. The use of adjuvant glucocorticoids reduces mortality among patients with other forms of meningitis in some populations, but their use is untested in patients with cryptococcal meningitis.
Methods: In this double-blind, randomized, placebo-controlled trial, we recruited adult patients with HIV-associated cryptococcal meningitis in Vietnam, Thailand, Indonesia, Laos, Uganda, and Malawi. All the patients received either dexamethasone or placebo for 6 weeks, along with combination antifungal therapy with amphotericin B and fluconazole.

Results: The trial was stopped for safety reasons after the enrollment of 451 patients. Mortality was 47% in the dexamethasone group and 41% in the placebo group by 10 weeks (hazard ratio in the dexamethasone group, 1.11; 95% confidence interval [CI], 0.84 to 1.47; P=0.45) and 57% and 49%, respectively, by 6 months (hazard ratio, 1.18; 95% CI, 0.91 to 1.53; P=0.20). The percentage of patients with disability at 10 weeks was higher in the dexamethasone group than in the placebo group, with 13% versus 25% having a prespecified good outcome (odds ratio, 0.42; 95% CI, 0.25 to 0.69; P<0.001). Clinical adverse events were more common in the dexamethasone group than in the placebo group (667 vs. 494 events, P=0.01), with more patients in the dexamethasone group having grade 3 or 4 infection (48 vs. 25 patients, P=0.003), renal events (22 vs. 7, P=0.004), and cardiac events (8 vs. 0, P=0.004). Fungal clearance in cerebrospinal fluid was slower in the dexamethasone group. Results were consistent across Asian and African sites.

Conclusions: Dexamethasone did not reduce mortality among patients with HIV-associated cryptococcal meningitis and was associated with more adverse events and disability than was placebo.

Abstract Full-text [free] access

Editor’s notes: Outcomes from cryptococcal meningitis in people living with HIV are very poor. This was highlighted here. Three out of five people overall had died or were severely disabled ten weeks after enrolment. This clinical trial provides strong evidence that steroids cause more harm than good and therefore routine use should not be recommended. Dexamethasone was not only associated with higher risk of death or disability but also with higher risk of significant adverse events, particularly bacterial sepsis.

The majority of deaths occurred early, in the first three weeks. Most participants were ART naïve and severely immunosuppressed (CD4+ cell count <50 cells/µL) and most deaths look to have occurred prior to the scheduled start of antiretroviral therapy. This may also partly explain the low frequency of immune reconstitution inflammatory syndrome (IRIS) and the lack of any observed benefit of dexamethasone in reducing IRIS.

Although dexamethasone was associated with greater decline in intracranial pressure, this did not translate into improved neurological outcomes. All participants had regular lumbar punctures for pressure monitoring. This might have limited the potential to observe a benefit from dexamethasone. Some explanation for the adverse outcomes might come from the impaired fungal clearance in cerebrospinal fluid – a marker of poor outcomes in previous studies. It should be noted that antifungal treatment in this trial was suboptimal. The combination of amphotericin and flucytosine was not used, despite evidence of improved outcomes and more rapid fungal clearance with this regimen.

While the search should go on for better treatment strategies, the findings in this study emphasise the importance of prevention, focused firmly, on earlier HIV diagnosis and treatment.

Methods: HIV-infected children aged ≤13 years with suspected intrathoracic tuberculosis were enrolled in 8 hospitals in Burkina Faso, Cambodia, Cameroon, and Vietnam. Gastric aspirates were taken for children aged <10 years and expectorated sputum samples were taken for children aged ≥10 years (standard samples); nasopharyngeal aspirate and stool were taken for all children, and a string test was performed if the child was aged ≥4 years (alternative samples). All samples were tested with Xpert®. The diagnostic accuracy of Xpert® for culture-confirmed tuberculosis was analyzed in intention-to-diagnose and per-protocol approaches.

Results: Of 281 children enrolled, 272 (96.8%) had ≥1 specimen tested with Xpert® (intention-to-diagnose population), and 179 (63.5%) had all samples tested with Xpert® (per-protocol population). Tuberculosis was culture-confirmed in 29/272 (10.7%) children. Intention-to-diagnose sensitivities of Xpert® performed on all, standard, and alternative samples were 79.3% (95% confidence interval [CI], 60.3-92.0), 72.4% (95% CI, 52.8-87.3), and 75.9% (95% CI, 56.5-89.7), respectively. Specificities were ≥97.5%. Xpert® combined on nasopharyngeal aspirate and stool had intention-to-diagnose and per-protocol sensitivities of 75.9% (95% CI, 56.5-89.7) and 75.0% (95% CI, 47.6-92.7), respectively.

Conclusions: The combination of nasopharyngeal aspirate and stool sample is a promising alternative to methods usually recommended by national programs. Xpert® performed on respiratory and stools samples enables rapid confirmation of tuberculosis diagnosis in HIV-infected children.

Abstract access

Editor’s notes: This article reports on a prospective cohort study of HIV-positive children (≤ 13 years) with suspected intrathoracic tuberculosis in eight hospitals in Burkina Faso, Cambodia, Cameroon, and Viet Nam. Diagnosis of tuberculosis among children is challenging because it is more difficult to obtain sputum, and their sputum often has fewer bacilli, requiring more sensitive tests. In 2014, WHO recommended scaling-up the use of Xpert® MTB/RIF among children. However, any test which is dependent on obtaining a sputum specimen will be suboptimal for diagnosis of tuberculosis in children.

In this study the investigators examined the feasibility of using alternative specimens with Xpert® MTB/ RIF for the diagnosis of tuberculosis in HIV-positive children. Using an intention-to-diagnose and a per-protocol analysis, they also assessed the diagnostic accuracy of Xpert® on nasopharyngeal aspirate and stool samples, using culture-confirmed tuberculosis as the reference standard.

The authors found that the performance of Xpert® in alternative samples was comparable to that of standard samples. They found excellent feasibility of obtaining samples of nasopharyngeal aspirates and stool, and a good sensitivity of Xpert® (~76%) when using that combination of samples. The authors suggested more research to simplify the processing of the stool samples for Xpert®, which would make the combination of both samples an attractive collection method for children unable to produce sputum.

Although Xpert® produces results relatively rapidly, some testing was done retrospectively, and only half of the Xpert® results were immediately available. As many children in this study had features of severe disease, it is not surprising that clinicians often started TB treatment immediately without waiting for results. Thus in practice the Xpert® result often provided bacteriological confirmation of a
clinical diagnosis for children who had already started TB treatment, although it did also lead to some TB treatment initiations.

Despite conducting this study over more than two years in eight hospitals, the final number of enrolled children with culture-confirmed tuberculosis was only 29. It would be interesting to know whether using Xpert® on alternative specimens from children had an impact on patient-important outcomes, particularly mortality, though this would have required a much larger study. Studies of Xpert® implementation among adults have found increased yield in terms of bacteriological diagnoses. However, most have not found an impact on patient-important outcomes. Several children died before all the protocol-required specimens could be obtained, emphasizing the importance of rapid and more sensitive TB diagnostic tests for severely-ill children.

Empiric TB treatment of severely ill patients with HIV and presumed pulmonary TB improves survival.


Rationale: In 2007, WHO issued emergency recommendations on empiric treatment of sputum acid-fast bacillus (AFB) smear-negative patients with possible tuberculosis (TB) in HIV-prevalent areas, and called for operational research to evaluate their effectiveness. We sought to determine if early, empiric TB treatment of possible TB patients with abnormal chest radiography or severe illness as suggested by the 2007 WHO guidelines is associated with improved survival.

Methods: We prospectively enrolled consecutive HIV-seropositive inpatients at Mulago Hospital in Kampala, Uganda, from 2007 to 2011 with cough ≥2 weeks. We retrospectively examined the effect of empiric TB treatment before discharge on eight-week survival among those with and without a WHO-defined "danger sign," including fever >39 degrees C, tachycardia >120 beats-per-minute, or tachypnea >30 breaths-per-minute. We modeled the interaction between empiric TB treatment and danger signs and their combined effect on eight-week survival and adjusted for relevant covariates.

Results: Among 631 sputum smear-negative patients, 322 (51%) had danger signs. Cumulative eight-week survival of patients with danger signs was significantly higher with empiric TB treatment (80%) than without (64%, p<0.001). After adjusting for duration of cough and concurrent hypoxemia, patients with danger signs who received empiric TB treatment had a 44% reduction in eight-week mortality (Risk Ratio 0.54, 95%CI 0.32-0.91, p=0.020).

Conclusions: Empiric TB treatment of HIV-seropositive, smear-negative, presumed pulmonary TB patients with one or more danger signs is associated with improved eight-week survival. Enhanced implementation of the 2007 WHO empiric-treatment recommendations should be encouraged whenever and wherever rapid and highly sensitive diagnostic tests for TB are unavailable.

Abstract access

Editor's notes: TB remains the most important cause of death among people living with HIV worldwide. Empirical TB treatment, meaning treatment without bacteriological confirmation, is common practice among people with symptoms suggesting TB, where diagnostic tests are unsatisfactory and the risk of death is high if TB were left untreated.

WHO recommends empirical TB treatment for people living with HIV who are seriously ill, for example as indicated by one or more “danger signs” (respiratory rate over 30 per minute, temperature over
39°C, pulse over 120, unable to walk unaided). However the evidence to guide the use of empirical TB treatment is very limited. This study adds to that evidence base. HIV-positive adult in-patients with a cough of at least two weeks duration were recruited as part of a study of pneumonia, in a referral hospital in Uganda, and underwent a standard set of investigations. This sub-analysis included people who were sputum smear negative, and investigated the association of empirical TB treatment with survival at eight weeks. Among individuals who had one or more danger signs, people who were treated for TB were more likely to be alive at eight weeks (80% versus 64%). Among people without danger signs, mortality was not associated with empirical TB treatment (survival at eight weeks, 76% among people treated empirically versus 74% among people not treated).

It is important to keep in mind that this was an observational cohort, not a randomised trial, and the implementation of empirical TB treatment according to WHO guidelines was far from complete. Among HIV-positive adults eligible for the study (cough for at least two weeks and sputum smear negative), over half had one or more danger signs, but only 23% of them received TB treatment. Some 20% of the people included in the study were already taking antiretroviral therapy (ART). It is implied that few started ART during admission, and this may also have contributed to high mortality.

This study is particularly relevant in the context of the results of two recent trials of empirical TB treatment. One, the REMEMBER trial will be discussed in next month’s digest. Briefly this study found no mortality benefit of empirical TB treatment over isoniazid preventive therapy among HIV-positive people with CD4 counts below 50 among whom locally-available diagnostic tests had not detected TB. The other trial, TB Fast Track, was presented at CROI in February. This trial found no difference in mortality among adult out-patients, with CD4 counts of 150 or fewer. The patients were managed according to a nurse-led algorithm using point of care tests to stratify TB risk. Immediate empirical TB treatment for people at highest risk was compared to standard management. The results of all these studies should lead to better definition of criteria for the use of empirical TB treatment. Ultimately, however, better tests for TB that can be used in primary care settings are urgently needed.

Evaluation of a public-sector, provider-initiated cryptococcal antigen screening and treatment program, western Cape, South Africa.


Background: Screening for serum cryptococcal antigen (CrAg) may identify those at risk for disseminated cryptococcal disease (DCD), and pre-emptive fluconazole treatment may prevent progression to DCD. In August 2012, the Western Cape Province (WC), South Africa, adopted provider-initiated CrAg screening. We evaluated the implementation and effectiveness of this large-scale public-sector program during its first year, September 1, 2012-August 31, 2013.

Methods: We used data from the South African National Health Laboratory Service, WC provincial HIV program, and nationwide surveillance data for DCD. We assessed the proportion of eligible patients screened for CrAg (CrAg test done within 30 days of CD4 date) and the prevalence of CrAg positivity. Incidence of DCD among those screened was compared with those not screened.

Results: Of 4395 eligible patients, 26.6% (n=1170) were screened. The proportion of patients screened increased from 15.9% in September 2012 to 36.6% in August 2013. The prevalence of positive serum CrAg was 2.1%. Treatment data were available for 13 of 24 CrAg-positive patients; nine of 13 were treated with fluconazole. Nine (0.8%) incident cases of DCD occurred among the 1170 patients who were screened for CrAg vs. 49 (1.5%) incident cases among the 3225 patients not screened (p=0.07).
Conclusions: Relatively few eligible patients were screened under the WC provider-initiated CrAg screening program. Unscreened patients were nearly twice as likely to develop DCD. CrAg screening can reduce the burden of DCD, but needs to be implemented well. To improve screening rates, countries should consider laboratory-based reflexive screening when possible.

Abstract access

Editor’s notes: Cryptococcus, a ubiquitous soil fungus, can cause cryptococcal meningitis (CM) or disseminated cryptococcal disease (DCD), which is often fatal among people with advanced HIV disease. Despite antiretroviral therapy availability, CM is now the leading cause of adult meningitis in sub-Saharan Africa with a mortality of up to 70% at 12 weeks in low-income settings. Asymptomatic individuals with a positive serum cryptococcal antigen (CrAg) and low CD4 counts are at a high risk of progression to disease. Identifying these individuals and initiating pre-emptive treatment to reduce morbidity and mortality forms the rationale for the inclusion of CrAg screening in the South African national guidelines.

This evaluation of the public sector provider-initiated CrAg screening and treatment programme in the western Cape revealed disappointing coverage during the first year of implementation. A laboratory-based reflex testing strategy, where the CrAg test is performed in the laboratory on any blood sample with CD4<100 may improve screening coverage. But, this requires adequate laboratory infrastructure and needs to be paired with optimal uptake of pre-emptive fluconazole among people with a positive CrAg result. In this study, uptake of fluconazole was lower than desired with about a third of eligible patients, for whom records were available, lacking any evidence of receiving fluconazole. In addition, a significantly higher proportion of people screened started ART compared with people who were not screened. This might partly explain the reduced incidence of cryptococcal disease in the screened group.

A stepped-wedge randomised trial evaluating CrAg screening in Uganda, presented at CROI 2016, found that one-third of persons with baseline CrAg titre of ≥1:160 died, despite receiving recommended pre-emptive fluconazole therapy. This suggests that semi-quantitative CrAg screening may be required to identify people at risk of death in whom more potent antifungal therapy may be necessary. The very high mortality in CrAg-positive patients despite antifungal therapy suggests that, for people at highest risk, CrAg screening should be implemented as part of a combined opportunistic infection screening and intervention package, including more intensive follow-up.

Community perceptions of community health workers (CHWs) and their roles in management for HIV, tuberculosis and hypertension in western Kenya.


Given shortages of health care providers and a rise in the number of people living with both communicable and non-communicable diseases, Community Health Workers (CHWs) are increasingly incorporated into health care programs. We sought to explore community perceptions of CHWs including perceptions of their roles in chronic disease management as part of the Academic Model Providing Access to Healthcare Program (AMPATH) in western Kenya. In depth interviews and focus group discussions were conducted between July 2012 and August 2013. Study participants were purposively sampled from three AMPATH sites: Chulaimbo, Teso and Turbo, and included patients within the AMPATH program receiving HIV, tuberculosis (TB), and hypertension (HTN) care, as well as caregivers of children with HIV, community leaders, and health care workers. Participants were asked to describe their perceptions of AMPATH CHWs,
including identifying the various roles they play in engagement in care for chronic diseases including HIV, TB and HTN. Data was coded and various themes were identified. We organized the concepts and themes generated using the Andersen-Newman Framework of Health Services Utilization and considering CHWs as a potential enabling resource. A total of 207 participants including 110 individuals living with HIV (n = 50), TB (n = 39), or HTN (n = 21); 24 caregivers; 10 community leaders; and 34 healthcare providers participated. Participants identified several roles for CHWs including promoting primary care, encouraging testing, providing education and facilitating engagement in care. While various facilitating aspects of CHWs were uncovered, several barriers of CHW care were raised, including issues with training and confidentiality. Suggested resources to help CHWs improve their services were also described. Our findings suggest that CHWs can act as catalysts and role models by empowering members of their communities with increased knowledge and support.

Abstract Full-text [free] access

Editor’s notes: As community-health workers are becoming an integrated part of the health care systems in Kenya, more information is required on how they are perceived by the communities they serve. This qualitative study explores perceptions on the role of community-health workers in chronic disease management.

Generally, community health workers are well received by the communities. They are perceived as an enabling resource in generating awareness on specific health issues and promoting positive health seeking behaviours. However, some negative perceptions were raised by several study participants, including their inability to maintain confidentiality and their sometimes limited or inaccurate knowledge on specific health issues, due to limited training.

Suggested resources to strengthen the role of community health workers in engaging communities in chronic disease management include additional training. Also information tools e.g. brochures, posters and charts and participation in larger communities’ awareness events e.g. through community gatherings. These findings are particularly useful for other community-health worker programmes to promote positive health seeking behaviours including successful linkage and retention in care.

Periodic presumptive treatment for vaginal infections may reduce the incidence of bacterial sexually transmitted infections.


Background: Bacterial vaginosis (BV) may increase women's susceptibility to sexually transmitted infections (STIs). In a randomized trial of periodic presumptive treatment (PPT) to reduce vaginal infections, we observed a significant reduction in BV. We further assessed the intervention effect on incident Chlamydia trachomatis (CT), Neisseria gonorrhoeae (GC), and Mycoplasma genitalium (MG).

Methods: Non-pregnant, HIV-uninfected women from the US and Kenya received intravaginal metronidazole 750mg plus miconazole 200mg or placebo for 5 consecutive nights each month for 12 months. Genital fluid specimens were collected every other month. Poisson regression models were used to assess the intervention effect on STI acquisition.

Results: Of 234 women enrolled, 221 had specimens available for analysis. Incidence of any bacterial STI (CT, GC, or MG) was lower in the intervention arm compared to placebo (incidence rate ratio [IRR]=0.54, 95% CI 0.32-0.91). When assessed individually, reductions in STIs were
but not statistically significant (CT: IRR=0.50, 95% CI 0.20-1.23; GC: IRR=0.56, 95% CI 0.19-1.67; MG: IRR=0.66, 95% CI 0.38-1.15).

**Conclusions:** In addition to reducing BV, this PPT intervention may also reduce women’s bacterial STI risk. Because BV is highly prevalent, often persists, and frequently recurs after treatment, interventions that reduce BV over extended periods could play a role in decreasing STI incidence globally.

**Abstract access**

**Editor’s notes:** Increasing attention is being paid to the health of vaginal microbiota. Disruption of the vaginal microbiota i.e. dysbiosis, is thought to increase susceptibility to other sexually transmitted infections, including HIV. While considerable observational data support the hypothesis of vaginal dysbiosis being a risk factor for sexually transmitted infection, the hypothesis has not been confirmed through randomized control trials. Women in the programme arm of this randomized control trial were presumptively treated for bacterial vaginosis and vulvovaginal candidiasis on a monthly basis. Relative to the control arm, the women in the programme arm had approximately half the risk of infection by Chlamydia trachomatis, Neisseria gonorrhoea or Mycoplasma genitalium. The findings provide strong evidence for considering healthy vaginal flora as a protective factor from sexually transmitted bacterial infections. Further research must consider whether the protection extends to sexually transmitted viruses and protozoa, and for adolescents and women who are not of African heritage.

**Evaluation of geospatial methods to generate subnational HIV prevalence estimates for local level planning.**

**Anderson SJ, Subnational Estimates Working Group of the HIVMC. AIDS. 2016 Feb 25. [Epub ahead of print]**

**Objective:** There is evidence of substantial subnational variation in the HIV epidemic. However, robust spatial HIV data are often only available at high levels of geographic aggregation and not at the finer resolution needed for decision making. Therefore, spatial analysis methods that leverage available data to provide local estimates of HIV prevalence may be useful. Such methods exist but have not been formally compared when applied to HIV.

**Design/methods:** Six candidate methods - including those used by UNAIDS to generate maps and a Bayesian geostatistical approach applied to other diseases - were used to generate maps and subnational estimates of HIV prevalence across three countries using cluster level data from household surveys. Two approaches were used to assess the accuracy of predictions: (1) internal validation, whereby a proportion of input data is held back (test dataset) to challenge predictions, (2) comparison with location specific data from household surveys in earlier years.

**Results:** Each of the methods can generate usefully accurate predictions of prevalence at unsampled locations, with the magnitude of the error in predictions similar across approaches. However, the Bayesian geostatistical approach consistently gave marginally the strongest statistical performance across countries and validation procedures.

**Conclusions:** Available methods may be able to furnish estimates of HIV prevalence at finer spatial scales than the data currently allow. The subnational variation revealed can be integrated into planning to ensure responsiveness to the spatial features of the epidemic. The Bayesian geostatistical approach is a promising strategy for integrating HIV data to generate robust local estimates.
Abstract access

**Editor’s notes:** Data from intensively monitored populations indicates that large differences in HIV prevalence can be seen across small geographic spaces. Understanding these localised spatial variations within a generalised epidemic can enable HIV programme resources to be used most effectively. However the data required for such localised estimation are often lacking. As a result modelling strategies must be used to predict local variation based on the best available data.

This study compares six different geospatial methods of estimating local HIV prevalence. The methods can be categorised by whether or not they use ancillary information such as road networks to improve their predictions and also whether they generated continuously changing prevalence surfaces (like map contours) or gave discrete estimates for geographic sub-regions e.g. districts.

While all methods produced reasonable overall levels of performance, those using a Bayesian geostatistical approach illustrated marginally better predictive accuracies. The levels of accuracy appeared more dependent on the national prevalence than the choice of model used.

The authors conclude by setting out a strategy for improvement of the models, principally through integrating additional data from sources such as antiretroviral therapy and prevention of mother-to-child transmission programmes, antenatal clinic surveys and case based reporting.