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

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1. Reduce sexual transmission


Background: Data on effectiveness of preexposure prophylaxis (PrEP) for human immunodeficiency virus (HIV)-uninfected women attempting conception with HIV-infected male partners are limited to observational studies.

Methods: To explore the benefits of PrEP for conception, we developed a model to estimate the average annual probability of a woman remaining HIV-uninfected and having a child ("successful" outcome) via condomless sex with an HIV-infected male. The outcome likelihood is dependent upon parameters defining HIV-1 infectivity. We simulated 2 scenarios: optimal (condomless sex acts limited to the ovulation window), and suboptimal (acts not limited to ovulation).

Results: In the optimal scenario when the male is on antiretroviral therapy (ART), the average annual probability of the successful outcome is 29.1%, increasing to 29.2% with the addition of PrEP (P = .45). In the suboptimal scenario, the probability is 26.8% with ART alone versus 27.3% with ART/PrEP (P < .0001). Older maternal age reduces the probability of success in both scenarios, particularly after age 30.

Conclusions: In our model, PrEP provides little added benefit when the HIV-infected male partner is on ART, condomless sex is limited to the ovulation window, and other modifiable transmission risks are optimized. Older female age decreases the probability of success by increasing the number of condomless sex acts required for conception.

Abstract access

Editor’s notes: Antiretrovirals (ARVs) have been shown in several studies to be highly effective in preventing both the acquisition of HIV in HIV negative individuals, and the transmission of HIV from HIV positive people to HIV negative people. However, the real-world application of these activities is still being investigated. This paper explores a strategy currently in discussion to use ARVs for safer conception in which the HIV negative partner might take pre-exposure prophylaxis (PrEP) and the HIV positive partner may be taking HIV treatment. The model employed in this paper looked specifically at the added benefit of the HIV negative woman taking PrEP. The results of the model illustrated that there was no added benefit of the woman taking PrEP if her HIV positive partner was taking HIV treatment consistently and they kept the number of condomless sex acts to the minimum required for the best chance of conception. Interestingly, as the woman in the model increases in age so do the number of condomless sex acts required to conceive, thus increasing the risk of acquiring HIV. While this paper illustrated that PrEP may not be worth the added expense, there may be situations where it still can provide added security to couples. Ultimately, models cannot completely account for what happens in real-life, and as the paper counsels, it will be up to physicians and their patients to decide what is best on a case by case basis.

A cluster randomized controlled trial to increase the availability and acceptability of voluntary medical male circumcision in Zambia: the Spear and Shield Project.

Background: Widespread voluntary medical male circumcision in Africa could avert an estimated 3.436 million HIV infections and 300,000 deaths over the next 10 years. Most Zambian men have expressed little interest in the procedure. **We tested the effect of the Spear and Shield intervention designed to increase demand for voluntary medical male circumcision among these hard-to-reach men.**

Methods: **This cluster randomised controlled trial was done between Feb 1, 2012, and Oct 31, 2014, in Lusaka, Zambia, where HIV prevalence is 20.8%.** 13 community health centres were stratified by HIV voluntary counselling and testing rates and patient census, and **randomly assigned (5:5:3) to experimental (the intervention), control, or observation-only conditions.** Community health centre health-care providers at all 13 sites received training in voluntary medical male circumcision. Eligible participants were aged at least 18 years, HIV-negative, uncircumcised, and had not proactively requested or planned for voluntary medical male circumcision at the time of enrolment. Trial statisticians did not participate in randomisation. After voluntary counselling and HIV testing, participants were recruited; female partners were invited to participate. **The primary outcomes at the individual level were the likelihood of voluntary medical male circumcision by 12 months post intervention, and condom use after voluntary medical male circumcision among participants receiving the intervention.** The trial is registered with ClinicalTrials.gov, number NCT01688167.

Findings: **800 uncircumcised HIV-negative men (400 in the experimental group, 400 in the control group) were enrolled. 161 participants in the experimental group and 96 in the control group had voluntary medical male circumcision (adjusted odds ratio 2.45, 95% CI 1.24–4.90; p=0.02).** Condom use was examined in participants who had voluntary medical male circumcision and reported sexual activity within 1 month of a post-circumcision assessment (88 in the experimental group and 64 in the control group). Condom use over time increased in the experimental group (p=0.03) but not in the control group (p=0.2). One patient died in each group; no adverse events related to study participation were reported.

Interpretation: **Comprehensive HIV prevention programmes can increase the demand for and uptake of voluntary medical male circumcision services.**

Abstract access

**Editor’s notes:** Voluntary medical male circumcision reduces the risk of HIV acquisition in men by approximately 60%, yet in some high-prevalence countries uptake is low. This presents challenges in meeting WHO targets of 80% coverage. In Zambia, only 37% of the national target has been achieved. In this cluster randomised trial, 13 community health centres were randomised to receive training in the “Spear and Shield” programme, control (training for an equivalent period of time on general disease prevention strategies) or observation only. The Spear and Shield programme consisted of four weekly 90 minute group sessions. Men in the programme group had about 2.5 times the odds of having male circumcision, compared to the control group participants. This increase in uptake of male circumcision was not associated with an increase in sexual risk behaviours. In fact there was an increase in condom use in the programme group. According to WHO, demand creation continues to be the major challenge in meeting male circumcision coverage goals. The authors propose that scaling up an evidence-informed programme such as Spear and Shield, while training community health care workers to perform circumcisions, might be one of the best and most cost-effective ways to significantly reduce HIV rates in high-incidence settings.

**Antiretroviral therapy availability and HIV disclosure to spouse in Rakai, Uganda: a longitudinal population-based study.**
Background: A decade after the rollout of antiretroviral therapy (ART) in sub-Saharan Africa, the effects of this structural change on social aspects of HIV, such as rates of HIV disclosure to partners, remain largely unmeasured. We evaluated whether the introduction of ART was associated with disclosure of HIV diagnosis to spouses in Rakai, Uganda, using longitudinal, population-based data.

Methods: We identified individuals in marital/cohabitating unions who were newly diagnosed with HIV in Rakai Community Cohort Study surveys between 2000 and 2008, where ART was introduced in mid-2004. Using discrete-time survival analysis, we assessed the hazard of self-reported HIV disclosure to spouse after diagnosis pre-ART and post-ART rollout, adjusting for individual and union characteristics. Disclosure in the ART period was further stratified by ART initiation.

Results: The analysis included 557 married adults, 264 of whom were diagnosed with HIV before ART was available (2000-2004), and 293 diagnosed after ART was introduced (2005-2008). The cumulative incidence of self-reported disclosure was 75.2% in the post-ART period, compared with 58.3% before ART availability [P < 0.001, adjusted hazard ratio: 1.46 (95% confidence interval: 1.16 to 1.83)]. In the post-ART period, observed disclosure rates were 39% (72 of 184) among those not in HIV care, 65% (82 of 126) among those in pre-ART care, and 85% (64 of 75) among persons on ART (P < 0.001).

Conclusions: Treatment availability and use, especially ART initiation, was associated with increased self-disclosure of HIV diagnosis to partners. ART access may facilitate the prevention of transmission to uninfected partners and linkage to treatment for infected couples.

Abstract access

Editor’s notes: For effective prevention of sexual transmission of HIV, it is important that individuals who are HIV positive disclose their status to their spouses and other sexual partners. However, anticipation of possible negative consequences of disclosure of HIV positive status can be a significant barrier to disclosure. Access to antiretroviral therapy (ART) has increased considerably in low- and middle-income countries since 2003. Longitudinal data on the effect of ART availability and HIV disclosure in general African populations is limited. This study investigated whether increased access to ART has had an impact on disclosure of newly diagnosed HIV infection to spouses by men and women in stable unions in Rakai, Uganda. Although the study population was relatively small, the investigators demonstrated availability of ART was associated with increased self-disclosure of HIV infection to a spouse. It is possible that some disclosures may have been unintended, as it would be difficult to conceal treatment, including frequent clinic visits, from a spouse or co-habiting partner. Even so, the increase in disclosures among both men and women was significant. Furthermore, the desire to access ART was documented as a motivating factor to disclose HIV diagnosis. Although a relatively high rate of disclosure was observed in this study, a substantial subset of adults had not shared their HIV diagnosis with their partners. This highlights the importance of supportive models of care, in addition to ART, to facilitate safe disclosure of HIV infection.

How long-distance truck drivers and villagers in rural southeastern Tanzania think about heterosexual anal sex: a qualitative study.
Objective: To explore ideas of truck drivers and villagers from rural Tanzania about heterosexual anal sex (HAS) and the associated health risks.

Methods: Qualitative study using 8 in-depth interviews (IDIs) and 2 focus group discussions (FGDs) with truck drivers and 16 IDIs and 4 FGDs with villagers from the Morogoro region. Study participants included 24 women and 46 men. Data analysis was performed thematically employing standard qualitative techniques.

Results: Reasons why men would practice HAS included sexual pleasure, the belief that anal sex is safer than vaginal sex, alternative sexual practice, exploration and proof of masculinity. Reasons why women would practice HAS included financial need, retaining a partner, alternative for sex during menses, pregnancy prevention and beauty enhancement because HAS is believed to ‘fatten the female buttocks’. Most participants believed that condoms are not needed during HAS. This was linked to the ideas that infections only ‘reside in wet places’ (vagina) and that the anus is not ‘conducive’ for condom use; condoms reduce ‘dryness’ and ‘friction’ (pleasure) and may ‘get stuck inside’.

Conclusions: The study participants reported practices and ideas about HAS that put them at risk for HIV and sexually transmitted infections. Greater attention to education about HAS is urgently needed in Tanzania, where this sexual practice is still regarded as a taboo. This study offers useful information that could be included in sex education programmes.

Abstract access

Editor's notes: This paper explores the views of truck drivers and villagers on heterosexual anal sex. During in-depth interviews and focus group discussions in the Morogoro region of the United Republic of Tanzania the researchers asked participants about their opinions on sexual practices more broadly and specifically on heterosexual anal sex. The findings reveal that the participants perceive that heterosexual anal sex is becoming a common practice. In discussing why men practice heterosexual anal sex, the participants suggested that sexual pleasure, fulfilment of ideas of masculinity, and sexual exploration were the main reasons. For women, however, the participants suggested that the main reasons were financial, maintaining their relationships, pregnancy prevention, for sex during menstruation, and ‘fattening female buttocks’. When asked about HIV protection, many participants did not perceive that condom protection was feasible or required during heterosexual anal sex. The findings, while based on perceptions of the behaviour of ‘others’ and not on own accounts, suggest that heterosexual anal sex is more widespread in Tanzania than often assumed. And if it is a widespread and unprotected sexual practice, it is an important route of HIV infection.

2. Eliminate new HIV infections among children

Reconstructing the PMTCT cascade using cross-sectional household survey data: The PEARL Study.

Background: Given the ambitious targets to reduce pediatric AIDS worldwide, ongoing assessment of programs to prevent mother-to-child HIV transmission (PMTCT) is critical. The concept of a "PMTCT cascade" has been used widely to identify bottlenecks in program implementation; however, most efforts to reconstruct the cascade have relied on facility-based approaches that may limit external validity.

Methods: We analyzed data from the PEARL household survey, which measured PMTCT effectiveness in 26 communities across Zambia, South Africa, Cote d'Ivoire, and Cameroon. We recruited women who reported a delivery in the past two years. Among mothers confirmed to be HIV-infected at the time of survey, we reconstructed the PMTCT cascade with self-reported participant information. We also analyzed data about the child's vital status; for those still alive, HIV testing was performed via DNA PCR.

Results: Of the 976 eligible women, only 355 (36%) completed every step of the PMTCT cascade. Among the 621 mother-child pairs who did not, 22 (4%) reported never seeking antenatal care, 103 (17%) were not tested for HIV during pregnancy, 395 (64%) reported testing but never received their HIV-positive result, 48 (8%) did not receive maternal antiretroviral prophylaxis, and 53 (9%) did not receive infant antiretroviral prophylaxis. The lowest prevalence of infant HIV infection or death was observed in those completing the cascade (10%, 95% CI: 7%-12%).

Conclusions: Future efforts to measure population PMTCT impact should incorporate dimensions explored in the PEARL Study - including HIV testing of HIV-exposed children in household surveys - to better understand program effectiveness.

Abstract access

Editor’s notes: Programmes to prevent the transmission of HIV from mother-to-child can virtually eliminate transmission when conducted with adequate coverage and quality. This population-based study recruited women living with HIV who had given birth in the past 24 months from four sub-Saharan African countries including Cameroon, Côte d'Ivoire, South Africa and Zambia. The 976 mothers allowed their children to be tested for HIV, and reported on the level of maternal health services they received for that child, the “prevention of mother-to-child HIV transmission cascade”. While 98% of mothers had at least one contact with antenatal care services, only 36% eventually received services considered to be adequate for preventing transmission of HIV to their children. This study is notable for highlighting exactly where coverage gaps exist along the treatment pathway. In particular, 53% of mothers did not receive the result of an HIV test, and so would not have received follow-up services to prevent transmission. As a population-based study, these data provide a fuller picture of service coverage which cannot be captured by traditional monitoring and evaluations systems. These results can inform where systems strengthening must occur along the “prevention of mother-to-child HIV transmission cascade”, so that transmission risk is minimized for all children born to women living with HIV.

3. 15 million accessing treatment

Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials.

Background: Tenofovir disoproxil fumarate can cause renal and bone toxic effects related to high plasma tenofovir concentrations. Tenofovir alafenamide is a novel tenofovir prodrug with a 90% reduction in plasma tenofovir concentrations. Tenofovir alafenamide-containing regimens can have improved renal and bone safety compared with tenofovir disoproxil fumarate-containing regimens.

Methods: In these two controlled, double-blind phase 3 studies, we recruited treatment-naive HIV-infected patients with an estimated creatinine clearance of 50 mL per min or higher from 178 outpatient centres in 16 countries. Patients were randomly assigned (1:1) to receive once-daily oral tablets containing 150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide (E/C/F/tenofovir alafenamide) or 300 mg tenofovir disoproxil fumarate (E/C/F/tenofovir disoproxil fumarate) with matching placebo. Randomisation was done by a computer-generated allocation sequence (block size 4) and was stratified by HIV-1 RNA, CD4 count, and region (USA or ex-USA). Investigators, patients, study staff, and those assessing outcomes were masked to treatment group. All participants who received one dose of study drug were included in the primary intention-to-treat efficacy and safety analyses. The main outcomes were the proportion of patients with plasma HIV-1 RNA less than 50 copies per mL at week 48 as defined by the US Food and Drug Administration (FDA) snapshot algorithm (pre-specified non-inferiority margin of 12%) and pre-specified renal and bone endpoints at 48 weeks. These studies are registered with ClinicalTrials.gov, numbers NCT01780506 and NCT01797445.

Findings: We recruited patients from Jan 22, 2013, to Nov 4, 2013 (2175 screened and 1744 randomly assigned), and gave treatment to 1733 patients (866 given E/C/F/tenofovir alafenamide and 867 given E/C/F/tenofovir disoproxil fumarate). E/C/F/tenofovir alafenamide was non-inferior to E/C/F/tenofovir disoproxil fumarate, with 800 (92%) of 866 patients in the tenofovir alafenamide group and 784 (90%) of 867 patients in the tenofovir disoproxil fumarate group having plasma HIV-1 RNA less than 50 copies per mL (adjusted difference 2.0%, 95% CI -0.7 to 4.7). Patients given E/C/F/tenofovir alafenamide had significantly smaller mean serum creatinine increases than those given E/C/F/tenofovir disoproxil fumarate (0.08 vs 0.12 mg/dL; p<0.0001), significantly less proteinuria (median % change -3 vs 20; p<0.0001), and a significantly smaller decrease in bone mineral density at spine (mean % change -1.30 vs -2.86; p<0.0001) and hip (-0.66 vs -2.95; p<0.0001) at 48 weeks.

Interpretation: Through 48 weeks, more than 90% of patients given E/C/F/tenofovir alafenamide or E/C/F/tenofovir disoproxil fumarate had virological success. Renal and bone effects were significantly reduced in patients given E/C/F/tenofovir alafenamide. Although these studies do not have the power to assess clinical safety events such as renal failure and fractures, our data suggest that E/C/F/tenofovir alafenamide will have a favourable long-term renal and bone safety profile.

Abstract access

Editor’s notes: Tenofovir alafenamide fumarate (TAF) is a new antiretroviral agent developed by Gilead Sciences and is closely related to tenofovir disoproxil fumarate (TDF). TDF is widely used, highly potent, and safe in the majority of people but long-term use has been associated with small risks of decreased kidney function, chronic kidney disease, and decreased bone mineral density. Both TAF and TDF are prodrugs of tenofovir but TAF achieves highly potent concentrations of
tenofovir inside HIV-relevant immune cells with much lower plasma concentrations than TDF. The lower plasma concentration of tenofovir associated with TAF is hypothesised to reduce the toxic effects with regards to kidney and bone health. TAF is also effective at the lower dose of 10-25 mg, compared with the standard TDF dose of 300mg per day. This may translate into lower drug costs if the lower dose required means lower manufacturing costs.

The authors report the combined results of two phase III, non-inferiority studies comparing the safety and effectiveness of TAF with TDF, funded by Gilead Sciences. In both studies, TAF was co-formulated into one, once-a-day tablet with elvitegravir, cobicistat and emtricitabine. There was a high rate of virologic suppression with the TAF-containing regimen, which was non-inferior to the TDF regimen. Compared to TDF, TAF had significantly more favourable effects on renal and bone parameters, with smaller decreases in creatinine clearance and bone mineral density and smaller increases in proteinuria. The real-world clinical significance of these findings remains to be seen but TAF-containing regimens may offer meaningful safety and cost benefits over TDF regimens in the long-term. The favourable characteristics of TAF have also led to the development of a sustained-release subcutaneous TAF implant, which has recently been evaluated in dogs. A long-acting TAF implant could have translational potential as a candidate for HIV prophylaxis in vulnerable populations.

Duration of antiretroviral therapy adherence interruption is associated with risk of virologic rebound as determined by real-time adherence monitoring in rural Uganda.


Methods: The Uganda AIDS Rural Treatment Outcomes Study is an observational longitudinal cohort of adults initiating ART. We monitored adherence with device that wirelessly transmits records of device openings, and routinely assessed HIV RNA quarterly. When 48+ hour lapses between device openings were detected, we made unannounced visits to participants to investigate the cause and assess HIV RNA. Generalized estimating equation logistic regressions were used to assess factors associated with viral rebound.

Results: We followed 479 participants (median 25 months per participant). Most were female (72%), median age was 36 years, median pre-ART CD4 count was 198 cells/µL, median pre-ART HIV RNA level was 5.0 log_{10} copies/ml, and median duration of prior viral suppression was 13 months. A total of 587 adherence interruptions followed confirmed prior viral suppression, of which 13 (2%) had detectable viral rebound. Viral rebound was associated with duration of adherence interruption (OR 1.25 for each day beyond 48 hours, p=0.007) and 30-day adherence prior to the interruption (OR 0.73, p=0.02).

Discussion: This paper is the first demonstration of HIV RNA rebound during adherence interruptions objectively measured in real-time. Odds of viral rebound increased by 25% with each day beyond 48 hours. Real-time adherence monitoring was feasible in a sub-Saharan African setting. Further research should assess the potential for real-time adherence interventions to sustain adherence to affordable first-line regimens.

Abstract access
Editor's notes: As the number of people taking antiretroviral therapy grows, the challenge of supporting retention and adherence to treatment becomes greater. Measuring adherence to treatment is difficult, particularly in resource-constrained settings. It is often based on self-report of missed pills, which lacks sensitivity. This paper reports a study in which adherence was monitored using a battery-operated pill box which electronically monitors each time the box is opened. Box opening is "reported" by short message service (SMS) either immediately or whenever the cellular network is next available. In this study, if the box was not opened for more than 48 hours, an unannounced home visit was made to investigate the cause and take blood for HIV viral load measurement.

Adherence of less than 80%, as measured by the adherence monitoring device, was associated with detectable viral load at the next routine clinic visit. Longer treatment interruptions were associated with increasing risk of HIV viral load being detectable in blood taken at the home visit. These results, based on a very small number of individuals with detectable viral load, are not unexpected. However the methodology is interesting in that these medication monitors have the potential to provide health care providers with real-time alerts concerning individuals missing doses. Medication monitors have previously been too expensive to be used outside research studies. However, there is interest in developing monitors which could be mass-produced at low cost. Such monitors have the potential to assist health workers in identifying individuals with poor adherence much more rapidly than is currently possible, and allowing additional adherence support to be targeted. As such they could play an important role in improving treatment outcomes.

Comparison of HBV-active HAART regimens in an HIV-HBV multinational cohort: outcomes through 144 weeks.


Objectives: To explore factors associated with short and long-term hepatitis B virus (HBV) DNA suppression in a multinational cohort of HIV-HBV co-infected patients receiving HBV-active antiretrovirals.

Methods: One hundred and fifteen HIV-HBV co-infected patients participating in one of the two global randomized clinical trials conducted by the Adult AIDS Clinical Trials Group of different antiretroviral regimens received either HBV monotherapy with either lamivudine or emtricitabine (N = 56), or HBV dual therapy with tenofovir disoproxil fumarate (TDF) + lamivudine or emtricitabine (N = 59).

Associations of pretreatment characteristics with the primary (HBV DNA <200 IU/ml at 24 weeks) and longitudinal outcomes through 144 weeks were explored using logistic regression. HBV drug-resistance mutations were determined by pol sequencing in those with viral rebound.

Results: The proportion with HBV DNA below 200 IU/ml was 60% (95% confidence interval 50-69%) at 24 weeks and 79% (95% confidence interval 69-88%) at 144 weeks. Pretreatment factors associated with the primary outcome were HBV DNA, CD4 T-cell count, and aspartate aminotransferase, but only pretreatment HBV DNA remained associated with long-term suppression (P < 0.0001). HBV therapy group was not significantly associated with the primary outcome at 24 weeks; however, longitudinally, a greater proportion in the dual-therapy group achieved HBV DNA below 200 IU/ml (P = 0.007). A higher proportion of hepatitis B e antigen-negative patients (n = 57) achieved HBV DNA below 200 IU/ml at any point, regardless of the therapy group. All 12 patients with emergence of lamivudine-resistant mutants were in the monotherapy group.
Conclusions: TDF-based dual HBV-active antiretroviral therapy is preferred to treat HIV-HBV co-infected patients. In resource-limited settings in which TDF may not be universally available, lamivudine or emtricitabine HBV monotherapy is a reasonable option in patients with low HBV replication.

Abstract access

Editor’s notes: Hepatitis B virus infection remains a leading cause of preventable morbidity and mortality globally, through cirrhosis and liver cancer. In settings with a high prevalence of HIV-HBV coinfection, there is an opportunity to optimise clinical management within the public health approach to antiretroviral therapy. This study adds to the evidence base suggesting that antiretroviral regimens containing lamivudine/emtricitabine and tenofovir are associated with better virologic outcomes than regimens without tenofovir for people co-infected with HIV and HBV. In this study, a post hoc analysis of two multicentre randomised controlled trials, regimens with two HBV-active agents provided more durable virologic suppression and limited the emergence of lamivudine-resistant HBV strains. Although recommendations about the treatment of HIV-HBV coinfection are incorporated into WHO antiretroviral guidelines, testing for HBV infection within antiretroviral programmes is still uncommon and tenofovir is not universally employed in standard first-line antiretroviral regimens. With an increasing number of people switching to second-line antiretroviral regimens, there is the additional challenge of identifying HBV infection in order to maintain HBV-active agents within the second-line regimen. There is now a need for better evidence around how to operationalise these recommendations within national antiretroviral programmes.

Impact of patient-selected care buddies on adherence to HIV care, disease progression and conduct of daily life among pre-antiretroviral HIV-infected patients in Rakai, Uganda: a randomized controlled trial.


Background: Data are limited on effects of household or community support persons ("care buddies") on enrolment into and adherence to pre-antiretroviral HIV care. We assessed the impact of care buddies on adherence to HIV clinic appointments, HIV progression and conduct of daily life among pre-ART HIV-infected individuals in Rakai, Uganda.

Methods: 1209 HIV infected pre-ART patients aged ≥15 years were randomized to standard of care (SOC) (n = 604) or patient-selected care buddy (PSCB) (n= 605) and followed at 6 and 12 months. Outcomes were adherence to clinic visits; HIV disease progression and self-reported conduct of daily life. Incidence and prevalence rate ratios and 95% confidence intervals (95%CI) were used to assess outcomes in the intent-to-treat and as-treated analyses.

Results: Baseline characteristics were comparable. In the ITT analysis both arms were comparable with respect to adherence to CD4 monitoring visits (adjPRR 0.99, 95%CI 0.93-1.04, p=0.625), and ART eligibility (adjPRR=1.00, 95%CI 0.77-1.31, p=0.946). Good conduct of daily life was significantly higher in the PSCB than the SOC arm (adjPRR 1.08, 95%CI 1.03-1.13, p=0.001). More men (61%) compared to women (30%) selected spouses/partners as buddies (p<0.0001.) 22% of PSCB arm participants discontinued use of buddies.
Conclusion: In pre-ART persons, having care buddies improved the conduct of daily life of the HIV infected patients but had no effect on HIV disease progression and only limited effect on clinic appointment adherence.

Abstract access

Editor’s notes: To maximise the impact of antiretroviral therapy (ART), people living with HIV should be diagnosed early, enrolled and retained in pre-ART care, initiated on ART promptly, and retained in ART care. Long-term adherence to achieve and maintain viral load suppression is the last step in the continuum of HIV care. Engagement along the complete HIV treatment cascade will determine the long-term success of the global response to HIV.

Like this one, the next article report on the results of randomized trials evaluating programmes to improve enrolment and retention into pre-ART care.

The first randomized trial assessed the impact of trained patient-selected care buddies among people living with HIV not yet on ART. The outcomes were adherence to HIV clinic appointments, HIV progression, and conduct of daily life (participants’ perception of their general health, pain and ability to perform activities of daily living) over a 12-month period. The authors found that having care buddies improved the conduct of life but had no effect on retention in care or HIV disease progression. Their findings indicate that it is not necessary for HIV programmes to delay HIV care while waiting for a patient to identify a care buddy. They also found that 22% of the participants discontinued the use of a care buddy, possibly due to buddy exhaustion after an extended period of time, while 10% of the participants in the control arm utilized the services of trained buddies. This will have diluted the difference between the arms and contributed to the lack of effect seen in the intention to treat analysis.

Interestingly the authors also report that women were less likely to select their spouse as a care buddy, some 30% versus 61% among men, likely because disclosure of HIV often carries adverse consequences for women, including domestic violence, abandonment and divorce.

The effect of community support agents on retention of people living with HIV in pre-antiretroviral care - A randomized controlled trial in Eastern Uganda.


Introduction: Over 50% of people living with HIV (PLHIV) in sub-Saharan Africa are lost to follow-up between diagnosis and initiation of antiretroviral treatment during pre-ARV care. The effect of providing home counselling visits by community support agents on 2-year retention in pre-ARV care was evaluated through a randomized controlled trial in eastern Uganda.

Methods: 400 newly screened HIV-positive persons were randomly assigned to receive post test counselling alone (routine arm), or post test counselling and monthly home counselling visits by community support agents to encourage them go back for routine pre-ARV care (intervention arm). The outcome measure was the proportion of new PLHIV in either arm who attended their scheduled pre-ARV care visits for at least six out of the anticipated 8 visits in the first 24 months after HIV diagnosis. The difference between the two study arms was assessed using chi-square and T-tests. Mantel-Haenszel Risk Ratios (MHRR) and multivariate logistic models were used to assess the adjusted effect of the intervention on the outcome.
Findings: In all models generated, participants receiving monthly home counselling visits were 2.5 times more likely to be retained in pre-ARV compared to those in standard care over a period of 24 months (ARR 2.5, 95% CI 2.0-3.0).

Interpretation: Monthly follow-up home visits by community workers more than doubled the retention of PLHIV in pre-ARV care in rural Uganda and can be applicable in similar resource-poor settings.

Abstract access

Editor’s notes: In this second randomized trial, the impact of repeated home counselling visits by community support agents (CSAs) on retention among patients not yet on ART was assessed.

In contrast to the previous article, the authors found a large effect on retention. Some 82% were retained in the programme arm at two years after a positive HIV test compared to 34% in the control arm (standard of care: clinic-based post-test counselling alone). The authors suggest that the improved health seeking behaviour and retention in care, could be explained by the CSAs acting as primary care linkages as they encouraged participants to go to the nearest health centre for HIV care. They also suggest that the excellent two year retention rates can be explained by the persistent monthly visits by the CSAs to the people living with HIV. The linkage function of the CSAs, which was not a function of the care buddies described in the first article, might further explain the different findings on retention.

The authors also report that clients in the programme arm were twice as likely to disclose their HIV status compared to clients in the control arm.

They conclude that community programmes that encourage status acceptance and disclosure should be further reinforced.

4. Avoid TB deaths

Immunity to measles, mumps and rubella in US children with perinatal HIV infection or perinatal HIV exposure without infection.


Background: Children with perinatal HIV infection (PHIV) may not be protected against measles, mumps and rubella because of impaired initial vaccine response or waning immunity. Our objectives were to estimate seroimmunity in PHIV and perinatally HIV-exposed but uninfected (HEU) children and identify predictors of immunity in the PHIV cohort.

Methods: PHIV and HEU were enrolled in the Pediatric HIV/AIDS Cohort Study (PHACS) at ages 7-15 years from 2007-2009. At annual visits, demographic, laboratory, immunization and clinical data were abstracted and serologic specimens were collected. Most recent serologic specimen was used to determine measles seroprotection by plaque-reduction neutralization assay and rubella seroprotection and mumps seropositivity by enzyme immunoassay. Sustained cART was defined as taking cART for at least 3 months.

Results: Among 428 PHIV and 221 HEU PHACS participants, the prevalence was significantly lower in PHIV children for measles seroprotection (57%[95% CI: 52-62%] vs. 99% [95% CI: 96-
rubella seroprotection (65% [95% CI: 60-70%] vs. 98% [95% CI: 95-100%]), and mumps seropositivity (59% [95% CI: 55-64%] vs. 97% [95% CI: 94-99%]). On multivariable analysis, greater number of vaccine doses while receiving sustained cART and higher nadir CD4 percentage between last vaccine dose and serologic testing independently improved the cumulative prediction of measles seroprotection in PHIV. Predictors of rubella seroprotection and mumps seropositivity were similar.

Conclusions: High proportions of PHIV children, but not HEU children, lack serologic evidence of immunity to measles, mumps and rubella, despite documented immunization and current cART. Effective cART before immunization is a strong predictor of current seroimmunity.

Abstract access

Editor’s notes: Administration of combination measles, mumps and rubella (MMR) vaccine has resulted in dramatic declines in these diseases. Children with HIV, however, may be susceptible to vaccine-preventable diseases despite immunisation, due to weaker or short-lived immunological responses following immunisation. Children living with HIV may be at higher risk of more severe disease. In addition, children who are susceptible to these diseases may contribute to community risk of outbreaks as control of measles, mumps and rubella depends upon a high proportion of the population being immune.

This study demonstrates that sero-protection to rubella and measles and sero-positivity to mumps was substantially lower among children with HIV aged seven to 15 years than among HIV-exposed but HIV-negative children. Notably, nearly all children with HIV in this study had received the full two-dose series of MMR vaccines, in contrast to previous studies where HIV infection has been a risk factor for failure to receive recommended immunisations. Also, despite concerns that HIV-exposed, but HIV-negative children may have subtle immunological abnormalities that could impair their responses to vaccines, the rates of sero-protection and sero-immunity in this group were high, and comparable to rates in the general population.

Previous studies have illustrated that immunosuppression, lack of antiretroviral therapy (ART) or incomplete HIV virologic suppression are associated with a poor response to vaccines. This study demonstrates that a high proportion of older children and youth (all infected perinatally) may not be protected against MMR despite achieving virologic suppression and good immune status with ART. Timing of receipt of MMR immunisation in relation to ART, but not overall number of vaccine doses, was independently associated with seropositivity to MMR vaccine. Children who received MMR doses after being on sustained ART had significantly higher levels of sero-positivity and sero-protection than children who received MMR vaccine before ART was instituted.

This study has important policy implications. ART coverage in children globally is still less than coverage in adults. Many children with HIV start ART only in older childhood. Early ART for children followed by the standard MMR schedule as well as repeating MMR vaccine dosing for older children, particularly children who received MMR vaccine prior to starting ART, will be important to avert the risk of these vaccine-preventable infections in this vulnerable population.

Implementation research to inform the use of Xpert MTB/RIF in primary health care facilities in high TB and HIV settings in resource constrained settings.

Background: The current cost of Xpert MTB RIF (Xpert) consumables is such that algorithms are needed to select which patients to prioritise for testing with Xpert.

Objective: **To evaluate two algorithms for prioritisation of Xpert in primary health care settings in a high TB and HIV burden setting.**

Method: Consecutive, presumptive TB patients with a cough of any duration were offered either Xpert or Fluorescence microscopy (FM) test depending on their CXR score or HIV status. In one facility, sputa from patients with an abnormal CXR were tested with Xpert and those with a normal CXR were tested with FM ("CXR algorithm"). CXR was scored automatically using a Computer Aided Diagnosis (CAD) program. In the other facility, patients who were HIV positive were tested using Xpert and those who were HIV negative were tested with FM ("HIV algorithm").

Results: Of 9482 individuals pre-screened with CXR, Xpert detected TB in 2090/6568 (31.8%) with an abnormal CXR, and FM was AFB positive in 8/2455 (0.3%) with a normal CXR. Of 4444 pre-screened with HIV, Xpert detected TB in 508/2265 (22.4%) HIV positive and FM was AFB positive in 212/1920 (11.0%) in HIV negative individuals. The notification rate of new bacteriologically confirmed TB increased; from 366 to 620/100 000/yr and from 145 to 261/100 000/yr at the CXR and HIV algorithm sites respectively. The median time to starting TB treatment at the CXR site compared to the HIV algorithm site was: 1(IQR 1-3 days) and 3 (2-5 days) (p<0.0001) respectively.

Conclusion: Use of Xpert in a resource-limited setting at primary care level in conjunction with prescreening tests reduced the number of Xpert tests performed. The routine use of Xpert resulted in additional cases of confirmed TB patients starting treatment. However, there was no increase in absolute numbers of patients starting TB treatment. Same day diagnosis and treatment commencement was achieved for both bacteriologically confirmed and empirically diagnosed patients where Xpert was used in conjunction with CXR.

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

**Editor’s notes:** Although many countries have begun to deploy molecular TB diagnostics, the cost of these technologies remains prohibitive for widespread use in low- and middle-income countries. This study in Zambian primary health care clinics aimed to explore whether the use of Xpert® MTB/RIF could be rationalised by pre-screening individuals with cough, either by chest X-ray (CXR) or by HIV testing. CXR screening only marginally reduced the use of Xpert® (as three-quarters of people screened had an abnormal CXR, using digital X-ray and computerised interpretation). Restricting use of Xpert® to those known to be HIV-positive reduced the number of Xpert® tests by around half. Under both algorithms, the proportion testing Xpert® positive was very high (22-32%), suggesting that too few people were being identified as needing TB investigation. Similar to other studies of Xpert® implementation, the overall number of people starting TB treatment did not increase with the introduction of Xpert®. However, the proportion of people starting TB treatment who had microbiological confirmation did increase substantially under both algorithms. Empirical TB treatment (meaning initiation of treatment without microbiological confirmation) remained common, in the X-ray algorithm particularly where a third of people with an abnormal CXR but a negative Xpert® were started on TB treatment. This study was not designed to determine how many people who genuinely had TB were missed by each algorithm. Also this paper did not include cost-effectiveness analyses. Based on this evidence, neither of these algorithms can be clearly recommended. Further evaluation of different screening and testing strategies will be important to inform the scale-up of molecular diagnostics.
5. Close the resource gap

Time and money: the true costs of health care utilization for patients receiving 'free' HIV/TB care and treatment in rural KwaZulu-Natal.


Background: HIV and TB services are provided free-of-charge in many sub-Saharan African countries, but patients still incur costs.

Methods: Patient-exit interviews were conducted with a representative sample of 200 HIV-infected patients not yet on ART (pre-ART), 300 ART patients, and 300 TB patients receiving public sector care in rural South Africa. For each group, we calculated health expenditures across different spending categories, time spent traveling to and utilizing services, and how patients financed their spending. Associations between patient group and costs were assessed in multivariate regression models.

Results: Total monthly health expenditures (7.3 South African Rand: 1 USD) were: 171 (95%CI 134-207) for pre-ART, 164 (95%CI 141-187) for ART, and 122 (95%CI 105-140) for TB patients. Total monthly time costs (in hours) were: 3.4 (95%CI 3.3-3.5) for pre-ART, 5.0 (95%CI 4.7-5.3) for ART and 3.2 (95%CI 2.9-3.4) for TB patients. **Though costs were similar across groups, pre-ART patients spent significantly more on traditional healers, chemists, and private doctors, while ART and TB patients spent more on transport to clinic visits. 31% of pre-ART, 39% of ART and 41% of TB patients borrowed money or sold assets to finance health costs.**

Conclusions: Patients receiving nominally free care for HIV/TB face large private costs. **Subsidized transport, fewer clinic visits, and drug pick-up points closer to home could reduce costs for ART patients, potentially improving adherence and retention.** Large expenditure on alternative care among pre-ART patients suggests that transitioning patients to ART earlier, as under TASP, may not impose substantial costs on patients.

Abstract access

**Editor’s notes:** At the time of this study, in 2010 in South Africa, people living with HIV and on antiretroviral therapy (ART) made monthly visits to the clinic to collect their medication and for clinic observation in their first year on ART. They visited every other month in subsequent years. People receiving TB treatment also attended the clinic once a month. People living with HIV who had not yet started ART visited the clinic every six or 12 months, depending on the CD4 cell count. The authors were surprised to find that for the third group, people who they term ‘pre-ART’, the costs of health care utilisation were roughly equivalent to the costs for people receiving monthly or bi-monthly ART and/or TB treatment. The difference is attributed in this paper to the time and money spent by people living with HIV yet to commence ART on traditional healers and self-medication. Hence, the conclusion that the earlier initiation of ART is unlikely to increase health utilisation costs. Indeed, alternative treatment schedules, with people on ART visiting health facilities less frequently as their years on treatment progress, can reduce costs further for people on ART. The assumption made in the paper is that pre-ART people starting treatment cease to access alternative care. Given the context of this study, where the authors claim that the use of alternative therapies for people on ART is not common, this may be correct. The possibility exists that given that data were collected through patient-exit interviews, people taking ART or TB medication may have been cautious about disclosing their use of alternative therapies. Concerns over sharing such information with interviewers attached
to a medical research organisation, are not uncommon. This is an area in need of further, mixed methods, research to investigate the ‘true costs of health care utilisation’. This current paper takes us a step towards that goal.

6. Eliminate stigma and discrimination

Change over time in police interactions and HIV risk behavior among female sex workers in Andhra Pradesh, India.


Little is known about the effectiveness of intervening to change interactions between female sex workers (FSWs) and police in order to reduce HIV risk. Using data collected in the context of a HIV prevention intervention that included components to change policing practices (n = 1680), we examine the association of FSWs’ reports of negative police interactions and HIV risk behaviors and whether these associations varied over time. Results show negative police interactions declined significantly over time. FSWs who had more than one negative police interaction were more likely to experience STI symptoms (AOR 2.97 [95 % CI 2.27-3.89]), inconsistently use condoms with their clients (AOR 1.36 [95 % CI 1.03-1.79]), and accept more money for condomless sex (AOR 2.37 [95 % CI 1.76-3.21]). Over time, these associations were stable or increased. Even where interventions have reduced the number of police incidents experienced by FSWs, stakeholders in HIV prevention must remain vigilant in challenging these incidents.

Abstract access

Editor’s notes: Laws relating to sex work are frequently ambiguous. This allows considerable police discretion about who to arrest and under what charges. Bribes and arrest both have real monetary costs for female sex workers, who are already usually economically vulnerable. Financial pressure and or poverty can push women into agreeing to riskier sex with riskier clients in riskier places. This paper examined if negative police experience is associated with increased HIV risk behaviours; and if negative police experience changed over time following comprehensive HIV prevention programming.

The study found negative police interactions in the previous six months were frequent. Police raided workplace (36.1%), police arrested respondent (14.5%), police accepted bribe or gift so respondent could avoid trouble (14.8%), police had sex with respondent so she could avoid trouble (11.1%) and police took condoms away (7.6%). Negative police interactions were linked with an increased HIV risk including STI symptoms in the past 12 months; inconsistent condom use with clients in the past seven days and accepting more money for sex without a condom. However, there was a reduction over time in the proportion of women experiencing one or more negative police interactions in the past six months (21.2% versus 16.2%). Risk behaviours also reduced over time.

This study adds to emerging literature that it is possible to intervene against violence exposure and negative police interaction as part of HIV prevention programming. It also underscores the importance of structural drivers in enhancing HIV risk among female sex worker populations.

Growing-up just like everyone else: key components of a successful pediatric HIV disclosure intervention in Namibia.
Objectives: To facilitate replication and adaptation of pediatric HIV disclosure interventions, we identified key components of a child-friendly cartoon book used to guide Namibian caregivers and healthcare workers (HCWs) through a gradual, structured disclosure process.

Design: Qualitative interviews were conducted with caregivers and HCWs from four high-volume pediatric HIV clinics in Namibia.

Methods: Semi-structured in-depth interviews with 35 HCWs and 64 caregivers of HIV+ children aged 7-15 were analyzed using constant comparative and modified grounded theory analysis. Major barriers to disclosure were compared to accounts of intervention success, and themes related to key components were identified.

Results: The disclosure book overcomes barriers to disclosure by reducing caregiver resistance, increasing HIV and disclosure knowledge, and providing a gradual, structured framework for disclosure. The delayed mention of HIV-specific terminology overcomes caregiver fears associated with HIV stigma, thus encouraging earlier uptake of disclosure initiation. Caregivers value the book's focus on staying healthy, keeping the body strong, and having a future 'like other kids', thus capitalizing on evidence of the positive benefits of resilience and hopefulness rather than the negative consequences of HIV. The book's concepts and images resonate with children who readily adopt the language of 'body soldiers' and 'bad guys' in describing how important it is for them to take their medicine. Discussion cues ease communication between HCWs, caregivers, and pediatric patients.

Conclusion: Given the urgent need for available pediatric HIV disclosure interventions, easily implementable tools like the Namibian disclosure book should be evaluated for utility in similar settings.

Editor's notes: There is clear guidance from global and national policy that school-aged children should be fully disclosed to about their positive HIV status. However in reality disclosure to children continues to be done at a much later stage and in an incomplete way. Simple activities are necessary to support carers to disclose, equipping them with appropriate ways to tell children what they need to know about their HIV status and the nature of their condition. This paper presents the findings from a qualitative study evaluating a child-friendly storybook activity in Namibia designed to facilitate and ease the challenges carers face in timely and full disclosure to children.

Both the caregivers and the healthcare workers reported that the book helped them overcome many of the barriers to disclosure. This finding suggests that the activity has considerable potential. The empirical literature focuses heavily on the reasons behind delayed disclosure including guilt, fear, and inadequate knowledge about how to approach and explain the topic. The particular value of this study is the contribution the authors are able to make to our understanding of what works to overcome these barriers to disclosure and why. They focus in particular on the use of metaphor within a narrative and the positive impact of a particular health behaviour (treatment adherence) in helping children to ameliorate the significance of the condition itself in their physical and social lives. What contributes to the success and applicability of the programme is that these books are designed to address common challenges faced by paediatric HIV clinics in resource-stretched settings with relative ease. For example the challenges posed by inconsistent caregivers accompanying the child to the clinic or the pressing demands on a healthcare worker's time in a busy clinic.
The evidence presented in this paper is based on self-report from the healthcare workers and carers. The study suggests that there would be considerable value in evaluating this programme through larger studies to assess its efficacy. However, in addition to that, asking children themselves, who have been exposed to the book, about their experiences in any future research would further strengthen our understanding of the impact of the programme in this setting. Involving the children in the research would inform how the programme can be refined and adapted for other settings.

HIV treatment scale-up and HIV-related stigma in sub-Saharan Africa: a longitudinal cross-country analysis.

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Objectives: We estimated the association between antiretroviral therapy (ART) uptake and HIV-related stigma at the population level in sub-Saharan Africa.

Methods: We examined trends in HIV-related stigma and ART coverage in sub-Saharan Africa during 2003 to 2013 using longitudinal, population-based data on ART coverage from the Joint United Nations Program on HIV/AIDS and on HIV-related stigma from the Demographic and Health Surveys and AIDS Indicator Surveys. We fitted 2 linear regression models with country fixed effects, with the percentage of men or women reporting HIV-related stigma as the dependent variable and the percentage of people living with HIV on ART as the explanatory variable.

Results: Eighteen countries in sub-Saharan Africa were included in our analysis. For each 1% increase in ART coverage, we observed a statistically significant decrease in the percentage of women (b = -0.226; P = .007; 95% confidence interval [CI] = -0.383, -0.070) and men (b = -0.281; P = .009; 95% CI = -0.480, -0.082) in the general population reporting HIV-related stigma.

Conclusions: An important benefit of ART scale-up may be the diminution of HIV-related stigma in the general population.

Abstract access

Editor’s notes: Focused on sub-Saharan Africa, this study suggests that a benefit of the scale-up of antiretroviral therapy (ART) may have been a reduction in HIV-associated stigma. The authors combine data on HIV-associated stigma from the Demographic and Health Surveys and AIDS Indicator Surveys with data on ART coverage from UNAIDS. The results are presented for each of 18 countries and the authors suggest that increases in ART coverage are correlated with decreasing stigma, especially among countries with high HIV prevalence. The authors hypothesise that by allowing a person with HIV to experience a healthier life, ART reduces the stigma of HIV’s association with moral deviance. The authors also attribute knowledge to decreases in stigma.

While addressing an interesting and important question, the paper has some limitations. We suggest that participant responses to questions about whether they would be willing to care for someone “sick with AIDS”, and whether they would want a family member to keep an AIDS diagnosis “secret” cannot safely be interpreted as reflecting stigmatising attitudes or anticipated stigma. It would have been interesting to know if the methods used in the analysis could assess the role of ART relative to other factors in being associated with any changes over time in HIV-associated stigma.