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

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   - Incentives for orphans to stay in school: a structural programme for HIV prevention in Zimbabwe
   - Context-specific combination HIV prevention for female sex workers
   - Using Facebook to increase uptake of HIV testing among MSM in Peru
   - Awareness of HIV status of self and partner – levels still too low
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   - Late antiretroviral therapy start persists for children under two years of age in low- and middle-income countries
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5. Strengthening HIV integration

- The impact of anti-retroviral treatment on home-based carers in Zambia

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UNAIDS
1. Reduce sexual transmission

Hormonal contraception and the risk of HIV acquisition: an individual participant data meta-analysis.


Background: Observational studies of a putative association between hormonal contraception (HC) and HIV acquisition have produced conflicting results. We conducted an individual participant data (IPD) meta-analysis of studies from sub-Saharan Africa to compare the incidence of HIV infection in women using combined oral contraceptives (COCs) or the injectable progestins depot-medroxyprogesterone acetate (DMPA) or norethisterone enanthate (NET-EN) with women not using HC.

Methods and findings: Eligible studies measured HC exposure and incident HIV infection prospectively using standardized measures, enrolled women aged 15-49 y, recorded ≥15 incident HIV infections, and measured prespecified covariates. Our primary analysis estimated the adjusted hazard ratio (aHR) using two-stage random effects meta-analysis, controlling for region, marital status, age, number of sex partners, and condom use. We included 18 studies, including 37 124 women (43 613 woman-years) and 1 830 incident HIV infections. Relative to no HC use, the aHR for HIV acquisition was 1.50 (95% CI 1.24-1.83) for DMPA use, 1.24 (95% CI 0.84-1.82) for NET-EN use, and 1.03 (95% CI 0.88-1.20) for COC use. Between-study heterogeneity was mild (I² < 50%). DMPA use was associated with increased HIV acquisition compared with COC use (aHR 1.43, 95% CI 1.23-1.67) and NET-EN use (aHR 1.32, 95% CI 1.08-1.61). Effect estimates were attenuated for studies at lower risk of methodological bias (compared with no HC use, aHR for DMPA use 1.22, 95% CI 0.99-1.50; for NET-EN use 0.67, 95% CI 0.47-0.96; and for COC use 0.91, 95% CI 0.73-1.41) compared to those at higher risk of bias (pinteraction = 0.003). Neither age nor herpes simplex virus type 2 infection status modified the HC-HIV relationship.

Conclusions: This IPD meta-analysis found no evidence that COC or NET-EN use increases women’s risk of HIV but adds to the evidence that DMPA may increase HIV risk, underscoring the need for additional safe and effective contraceptive options for women at high HIV risk. A randomized controlled trial would provide more definitive evidence about the effects of hormonal contraception, particularly DMPA, on HIV risk.

Abstract Full-text [free] access

Editor’s notes: As seen in the paper published this month by Ralph et al, observational studies have reported that hormonal contraception, in particular injectable progestins depot-medroxyprogesterone acetate (DMPA), may increase risk of HIV infection. This individual patient data meta-analysis adds further to the evidence. A major strength of the study is the large sample size. It provides sufficient power to examine associations between specific contraceptives and HIV risk and to investigate effect modification in pre-specified sub-group analyses. Furthermore, using individual-level data allowed a consistent approach to coding and adjustment for confounding. If the association is real, this has important implications for sexual and reproductive health in areas of sub-Saharan Africa where the incidence of HIV acquisition and unintended pregnancy is high.
Hormonal contraceptive use and women’s risk of HIV acquisition: a meta-analysis of observational studies.


Background: The evidence from epidemiological research into whether use of hormonal contraception increases women’s risk of HIV acquisition is inconsistent. We did a robust meta-analysis of existing data to provide summary estimates by hormonal contraceptive method which can be used to inform contraceptive guidelines, models, and future studies.

Methods: We updated a recent systematic review to identify and describe studies that met inclusion criteria. To ensure inclusion of more recent research, we searched PubMed for articles published after December, 2011, using the terms “hormonal contraception”, “HIV/acquisition”, “injectables”, “progestin”, and “oral contraceptive pills”. We assessed statistical heterogeneity for these studies, and, when appropriate, combined point estimates by hormonal contraception formulation using random-effects models. We assessed publication bias and investigated heterogeneity through subgroup and stratified analyses according to study population and design features.

Findings: We identified 26 studies, 12 of which met inclusion criteria. There was evidence of an increase in HIV risk in the ten studies of depot medroxyprogesterone acetate (pooled hazard ratio [HR] 1.40, 95% CI 1.16-1.69). This risk was lower in the eight studies done in women in the general population (pooled HR 1.31, 95% CI 1.10-1.57). There was substantial between-study heterogeneity in secondary analyses of trials (n=7, I2 51.1%, 95% CI 0-79.3). Although individual study estimates suggested an increased risk, substantial heterogeneity between two studies done in women at high risk of HIV infection (I2 54%, 0-88.7) precluded pooling estimates. There was no evidence of an increased HIV risk in ten studies of oral contraceptive pills (pooled HR 1.00, 0.86-1.16) or five studies of norethisterone enanthate (pooled HR 1.10, 0.88-1.37).

Interpretation: Our findings show a moderate increased risk of HIV acquisition for all women using depot medroxyprogesterone acetate, with a smaller increase in risk for women in the general population. Whether the risks of HIV observed in our study would merit complete withdrawal of depot medroxyprogesterone acetate needs to be balanced against the known benefits of a highly effective contraceptive.

Abstract access

Editor’s notes: This meta-analysis has similar findings to the individual patient data (IPD) meta-analysis by Morrison et al, also published this month. The study finds that depot medroxyprogesterone (DMPA) is associated with a moderate increase in HIV risk, and little evidence of a risk associated with combined oral contraceptives or norethisterone enanthate (NET-EN). The policy implications of this finding are unclear. As with the IPD analysis, this meta-analysis is based on observational studies and does not provide conclusive evidence that DMPA causes the increased risk of HIV. However, it does provide refined estimates for modelling studies to assess the implications of possible withdrawal of DMPA on maternal and HIV-associated mortality, so that context-specific contraceptive policies can be considered.

The impact of school subsidies on HIV-related outcomes among adolescent female orphans.

Purpose: We examine effects of school support as a structural HIV prevention intervention for adolescent female orphans in Zimbabwe after 5 years.

Methods: Three hundred twenty-eight orphan adolescent girls were followed in a clustered randomized controlled trial from 2007 to 2010. The experimental group received school fees, uniforms, and school supplies and were assigned a school-based "helper." In 2011-2012, the control group received delayed partial treatment of school fees only. At the final data point in 2012, survey, HIV, and Herpes Simplex Virus Type 2 (HSV-2) biomarker data were collected from approximately 88% of the sample. Bivariate and multivariate analyses were conducted on end point outcomes, controlling for age, religious affiliation, and baseline socioeconomic status.

Results: The two groups did not differ on HIV or HSV-2 biomarkers. The comprehensive 5-year intervention continued to reduce the likelihood of marriage, improve school retention, improve socioeconomic status (food security), and marginally maintain gains in quality of life, even after providing school fees to the control group.

Conclusions: Paying school fees and expenses resulted in significant improvements in life outcomes for orphan adolescent girls. Biological evidence of HIV infection prevention, however, was not observed. Our study adds to the growing body of research on school support as HIV prevention for girls in sub-Saharan Africa, but as yet, no clear picture of effectiveness has emerged.

Abstract access

Editor’s notes: Structural programmes for HIV prevention potentially offer a means to mitigate the risk factors which are thought to drive the substantially higher rates of HIV observed among adolescent women in low-income settings. In Zimbabwe, female orphans in the programme arm of this randomized control trial were offered a package of school support. This included payment of their school fees. There was low power to assess differences in HIV or HSV-2 prevalence by arm, but there were promising impacts on several important mediating factors for HIV infection. These included sexual debut, marriage, school drop-out, and socioeconomic status. The long follow-up period of five years and the high rate of retention in the study, 88%, are major strengths of this study. The study joins a limited evidence base on structural programmes for adolescent women in sub-Saharan Africa. Future research must re-consider the pathways by which structural determinants of HIV infection operate.

Combination HIV prevention for female sex workers: what is the evidence?


Sex work occurs in many forms and sex workers of all genders have been affected by HIV epidemics worldwide. The determinants of HIV risk associated with sex work occur at several levels, including individual biological and behavioural, dyadic and network, and community and social environmental levels. Evidence indicates that effective HIV prevention packages for sex workers should include combinations of biomedical, behavioural, and structural interventions tailored to local contexts, and be led and implemented by sex worker communities. A model simulation based on the South African heterosexual epidemic suggests that condom promotion and distribution programmes in South Africa have already reduced HIV incidence in sex workers and their clients by more than 70%. Under optimistic model assumptions, oral pre-exposure prophylaxis together with test and treat programmes could further reduce HIV incidence in South African sex workers and their clients by up to 40% over a 10-year period. Combining these biomedical
approaches with a prevention package, including behavioural and structural components as part of a community-driven approach, will help to reduce HIV infection in sex workers in different settings worldwide.

Abstract access

Editor’s notes: Sex workers live within complex contexts of risk when it comes to HIV, other STIs and diseases, and life more broadly. But relatively few large-scale HIV prevention programmes exist for female sex workers. This paper presents a framework for combination HIV prevention among female sex workers. The paper evaluates the effect of activities at the individual, sexual/social network, community, and public policy levels. It models the impact of combining more established individual and structural approaches with biomedical approaches. These include earlier treatment and vaginal or oral PrEP, in South Africa. The model simulations suggest that individual and structural programmes, including condom promotion and distribution programmes, and community-led initiatives, are key in reducing HIV incidence among female sex workers and their clients in South Africa. Expansion of voluntary, effective earlier treatment, together with PrEP could further reduce HIV incidence in this setting.

The HOPE social media intervention for global HIV prevention in Peru: a cluster randomised controlled trial.


Background: Social media technologies offer new approaches to HIV prevention and promotion of testing. We examined the efficacy of the Harnessing Online Peer Education (HOPE) social media intervention to increase HIV testing among men who have sex with men (MSM) in Peru.

Methods: In this cluster randomised controlled trial, Peruvian MSM from Greater Lima (including Callao) who had sex with a man in the past 12 months, were 18 years of age or older, were HIV negative or serostatus unknown, and had a Facebook account or were willing to create one (N=556) were randomly assigned (1:1) by concealed allocation to join intervention or control groups on Facebook for 12 weeks. For the intervention, Peruvian MSM were trained and assigned to be HIV prevention mentors (peer-leaders) to participants in Facebook groups. The interventions period lasted 12 weeks. Participants in control groups received an enhanced standard of care, including standard offline HIV prevention available in Peru and participation in Facebook groups (without peer leaders) that provided study updates and HIV testing information. After accepting a request to join the groups, continued participation was voluntary. Participants also completed questionnaires on HIV risk behaviours and social media use at baseline and 12 week follow-up. The primary outcome was the number of participants who received a free HIV test at a local community clinic. The facebook groups were analysed as clusters to account for intracluster correlations. This trial is registered with ClinicalTrials.gov, number NCT01701206.

Findings: Of 49 peer-leaders recruited, 34 completed training and were assigned at random to the intervention Facebook groups. Between March 19, 2012, and June 11, 2012, and Sept 26, 2012, and Dec 19, 2012, 556 participants were randomly assigned to intervention groups (N=278) or control groups (N=278); we analyse data for 252 and 246. 43 participants (17%) in the intervention group and 16 (7%) in the control groups got tested for HIV (adjusted odds ratio 2.61, 95% CI 1.55–4.38). No adverse events were reported.
Interpretation: Development of peer-mentored social media communities seemed to be an efficacious method to increase HIV testing among high-risk populations in Peru. Results suggest that the HOPE social media intervention could improve HIV testing rates among MSM in Peru.

Editor’s notes: Community peer-led HIV programmes aim to increase behaviours by changing social norms and attitudes. They have led to increased condom use and decreased unprotected anal intercourse. In this study, a peer-led social media activity was shown to increase HIV testing among men who have sex with men in Peru. The programme involved belonging to a closed Facebook group, with a peer-leader providing posts and chats about the importance of HIV testing and prevention. Further, the communities remained highly engaged in group discussions, suggesting that the activity may also work on improving linkage to care, although this was not an outcome in this trial. This study is the first social media-based randomised controlled trial assessing HIV testing and suggests the efficacy of using social media and other innovative low-cost technologies for HIV prevention and treatment in other settings.

Who knows their partner’s HIV status? Results from a nationally representative survey in Uganda.


Objective: We examine the extent to which Ugandans accurately know their HIV status and that of their partners.

Methods: The 2011 Uganda AIDS Indicator Survey (UAIS) was a nationally representative study of 15-59 year olds that tested 21366 individuals for HIV. We compared self-reported with UAIS determined HIV status for respondents. We were able to link 3285 couples in the survey and in this group we compared the reported HIV status of partners with that determined by UAIS. Multiple logistic regression analysis was used to identify factors associated with inaccurate knowledge of HIV status.

Results: An estimated 55.8% of adult Ugandans reported having had an HIV test. Of 1495 HIV-infected Ugandans, 59.1% were unaware of their HIV-infection. Among 3285 linked couples in this analysis, 273 (8.3%) couples had at least one infected partner; with 96 (2.9%) couples having both members infected and the remaining 177 couples (5.4%) being HIV discordant. This meant that 369 persons in the linked couple group had an HIV-infected partner. 110 (29.8%) of this group knew their partner was HIV infected. In multiple logistic regression analysis, accurately knowing that one’s partner was HIV infected was strongly associated with couple HIV testing (AOR 4.3, CI: 2.2-8.4) and reporting oneself to be HIV-positive, versus reporting HIV-negative (AOR 7.3, CI 3.8-14.3) or HIV status unknown (AOR 30.6, CI 3.8-263.4).

Conclusions: Respondents may be reporting the HIV status of their partners based on their own HIV status. Campaigns to inform people about the prevalence of serodiscordance in conjunction with further promotion of couple counseling may help increase the proportion of Ugandans who know their own HIV status and that of their partners.

Abstract access
Editor’s notes: It is important for people to know their own HIV status, and that of their partners, if HIV transmission reduction strategies are to be effective. In this large, nationally-representative survey in Uganda, self-reported HIV status was compared with laboratory-confirmed results. The proportion of women and men reporting to know their HIV status has increased considerably since the last survey. Yet over half of adults living with HIV were unaware of their HIV status. Less than a third of people with a partner living with HIV were aware of their partner’s status. There was a strong association between self-reported HIV status and reported partners’ HIV status. The authors suggest that one explanation may be that people are reporting the HIV status of their partners based on their own HIV status. This argument is supported by previous studies suggesting that concordance of HIV test results is often assumed. This study indicates a need for education strategies about the prevalence and consequences of discordance. These could be combined with couple testing and antiretroviral therapy as prevention, for discordant couples, to address the generalized HIV epidemic in Uganda and more widely.

Estimating the cost-effectiveness of pre-exposure prophylaxis to reduce HIV-1 and HSV-2 incidence in HIV-serodiscordant couples in South Africa.


Objective: To estimate the cost-effectiveness of daily oral tenofovir-based PrEP, with a protective effect against HSV-2 as well as HIV-1, among HIV-1 serodiscordant couples in South Africa.

Methods: We incorporated HSV-2 acquisition, transmission, and interaction with HIV-1 into a microsimulation model of heterosexual HIV-1 serodiscordant couples in South Africa, with use of PrEP for the HIV-1 uninfected partner prior to ART initiation for the HIV-1 infected partner, and for one year thereafter.

Results: We estimate the cost per disability-adjusted life-year (DALY) averted for two scenarios, one in which PrEP has no effect on reducing HSV-2 acquisition, and one in which there is a 33% reduction. After a twenty-year intervention, the cost per DALY averted is estimated to be $10,383 and $9,757, respectively - a 6% reduction, given the additional benefit of reduced HSV-2 acquisition. If all couples are discordant for both HIV-1 and HSV-2, the cost per DALY averted falls to $14,45, which shows that the impact is limited by HSV-2 concordance in couples.

Conclusion: After a 20-year PrEP intervention, the cost per DALY averted with a reduction in HSV-2 is estimated to be modestly lower than without any effect, providing an increase of health benefits in addition to HIV-1 prevention at no extra cost. The small degree of the effect is in part due to a high prevalence of HSV-2 infection in HIV-1 serodiscordant couples in South Africa.

Abstract Full-text [free] access

Editor’s notes: Herpes simplex virus-2 (HSV-2) is a risk factor for HIV, and can also have serious consequences for pregnant women if contracted during pregnancy. It is also difficult to prevent outside of condom use, and highly prevalent in sub-Saharan Africa. It is unsurprising then, that a great deal of enthusiasm came out of findings from the Partners pre-exposure prophylaxis (PrEP) Study, which found that daily oral emtricitabine/tenofovir disoproxil fumarate (TDF/FTC) decreased acquisition of HSV-2 by 33%. It also decreased the risk of HIV acquisition by some 75%. This article
evaluates the cost-effectiveness of oral tenofovir-based PrEP. It focuses on the incremental cost-effectiveness of reduction of HSV-2 incidence, an increased health benefit with no extra cost.

Surprisingly, the authors found that over a 20 year period, the efficacy of TDF/FTC PrEP to prevent HSV-2 infections will not materially affect the cost-effectiveness of PrEP. Although the simulated PrEP programme, with a 33% reduction in HSV-2 acquisition was more effective, it only had a minimal effect on the cost per DALY averted. This was compared to PrEP with 0% reduction in HSV-2 ($9757 as compared to $10 383/DALY averted). This is due to the relatively mild health consequences of HSV-2 in comparison with HIV. The vast majority of DALYs averted from the programme originate from preventing new HIV infections, rather than HSV-2 prevention. Nonetheless, the authors argue that this added health benefit may be appealing, particularly for dually discordant couples; one partner having both HIV and HSV-2. The authors also argue for further investigation of the impact of this combination for other populations, such as young women.

Efficacy of a savings-led microfinance intervention to reduce sexual risk for HIV among women engaged in sex work: a randomized clinical trial.


Objectives: We tested whether a structural intervention combining savings-led microfinance and HIV prevention components would achieve enhanced reductions in sexual risk among women engaging in street-based sex work in Ulaanbaatar, Mongolia, compared with an HIV prevention intervention alone.

Methods: Between November 2011 and August 2012, we randomized 107 eligible women who completed baseline assessments to either a 4-session HIV sexual risk reduction intervention (HIVSRR) alone (n = 50) or a 34-session HIVSRR plus a savings-led microfinance intervention (n = 57). At 3- and 6-month follow-up assessments, participants reported unprotected acts of vaginal intercourse with paying partners and number of paying partners with whom they engaged in sexual intercourse in the previous 90 days. Using Poisson and zero-inflated Poisson model regressions, we examined the effects of assignment to treatment versus control condition on outcomes.

Results: At 6-month follow-up, the HIVSRR plus microfinance participants reported significantly fewer paying sexual partners and were more likely to report zero unprotected vaginal sex acts with paying sexual partners.

Conclusions: Findings advance the HIV prevention repertoire for women, demonstrating that risk reduction may be achieved through a structural intervention that relies on asset building, including savings, and alternatives to income from sex work.

Abstract access

Editor’s notes: This study on sexual risk among sex workers in Ulaanbaatar, Mongolia, contributes to evidence that economic empowerment reduces HIV risk. Mongolia has a low prevalence of HIV. But it is considered highly vulnerable to the spread of HIV. This suggests that such programmes should be implemented to prevent concentrated epidemics becoming generalised epidemics. The authors acknowledge that while microfinance might be economically empowering it may represent “saving down”, which can keep women in debt and in a cycle of poverty and a reliance on sex work. The trial tested whether increasing financial literacy, business development knowledge and skills and personal savings would lead to more significant reductions in sexual risk behaviours than a sexual risk reduction programme alone. Groups of sex workers were randomised to receive either a four session
HIV sexual risk reduction programme (HIVSRR) or HIVSRR plus a savings-led microfinance programme. The HIVSRR alone involved the delivery of two sessions per week for two weeks and focused on skills to develop self-efficacy for risk reduction. The HIVSRR plus savings-led microfinance programme involved the four sessions on self-efficacy for risk reduction, followed by 12 financial literacy sessions three times a week and then 12 sessions of business development training three times a week. The activities were tested at three months and six months to explore the short time impact on sexual risk. The authors found that women who received the HIVSRR plus savings-led microfinance programme reported greater reductions in number of paying sexual partners and fewer sexual partners at six months follow up. These women were also more likely to report no unprotected vaginal sex acts at six months follow up. This study is important in illustrating that as a structural programme, the provision of microfinance is more effective if women are provided with skills to manage finances and to save money instead of ending up in a cycle of debt repayment. This has important implications for other microfinance programmes, such as programmes to reduce gender-based violence.

2. 15 million accessing treatment

Partner-based adherence intervention for second-line antiretroviral therapy (ACTG 5234): a multinational randomised trial.


Background: Adherence is key to the success of antiretroviral therapy. Enhanced partner support might benefit patients with previous treatment failure. We aimed to assess whether an enhanced partner-based support intervention with modified directly observed therapy would improve outcomes with second-line therapy in HIV-infected patients for whom first-line therapy had failed.

Methods: We did a multicentre, international, randomised clinical trial at nine sites in Botswana, Brazil, Haiti, Peru, South Africa, Uganda, Zambia, and Zimbabwe. Participants aged 18 years or older for whom first-line therapy had failed, with HIV RNA concentrations greater than 1000 copies per mL and with a willing partner, were randomly assigned (1:1), via computer-generated randomisation, to receive partner-based modified directly observed therapy or standard of care. Randomisation was stratified by screening HIV RNA concentration (≤10 000 copies per mL vs >10 000 copies per mL). Participants and site investigators were not masked to group assignment. Primary outcome was confirmed virological failure (viral load >400 copies per mL) by week 48. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00608569.

Findings: Between April 23, 2009, and Sept 29, 2011, we randomly assigned 259 participants to the modified directly observed therapy group (n=129) or the standard-of-care group (n=130). 34 (26%) participants in the modified directly observed therapy group achieved the primary endpoint of virological failure by week 48 compared with 23 (18%) participants in the standard-of-care group. The Kaplan-Meier estimated cumulative probability of virological failure by week 48 was 25-1% (95% CI 17·7–32·4) in the modified directly observed therapy group and 17·3% (10·8–23·7) in the standard-of-care group, for a weighted difference in standard of care versus modified directly observed therapy of −6·6% (95% CI −16·5% to 3·2%; p=0·19). 36 (14%) participants
reported at least one grade 3 or higher adverse event or laboratory abnormality (n=21 in the modified directly observed therapy group and n=15 in the standard-of-care group).

Interpretation: Partner-based training with modified directly observed therapy had no effect on virological suppression. The intervention does not therefore seem to be a promising strategy to increase adherence. Intensive follow-up with clinic staff might be a viable approach in this setting.

Abstract access

Editor’s notes: High rates of virologic failure on second-line antiretroviral therapy (ART) are reported in resource-limited settings. The main driver of this is thought to be sub-optimal adherence rather than resistance. As many of these settings have limited access to third-line regimens there is an urgent need for evidence-informed programmes to optimise peoples’ adherence, both to first-line and second-line regimens.

The results from this randomised controlled trial provide further evidence that partner-based modified directly observed therapy is not the answer. Interestingly, people enrolled in this trial had far lower rates of virologic failure than have been observed in programmatic settings, regardless of whether they were in the programme or standard-of-care arm. Many factors could account for this, including the fact that all people enrolled in the study had to have disclosed their status to a friend or family member, all received enhanced education and support and all attended regular clinic appointments. Further pragmatic studies which focus on clinic-and patient-level programmes are needed to determine the optimal strategies for maximising peoples’ adherence.

Immunodeficiency in children starting antiretroviral therapy in low-, middle-, and high-income countries.


Background: The CD4 cell count or percent (CD4%) at the start of combination antiretroviral therapy (cART) is an important prognostic factor in children starting therapy and an important indicator of program performance. We describe trends and determinants of CD4 measures at cART initiation in children from low-, middle-, and high-income countries.

Methods: We included children aged <16 years from clinics participating in a collaborative study spanning sub-Saharan Africa, Asia, Latin America, and the United States. Missing CD4 values at cART start were estimated through multiple imputation. Severe immunodeficiency was defined according to World Health Organization criteria. Analyses used generalized additive mixed models adjusted for age, country, and calendar year.

Results: A total of 34 706 children from 9 low-income, 6 lower middle-income, 4 upper middle-income countries, and 1 high-income country (United States) were included; 20 624 children (59%) had severe immunodeficiency. In low-income countries, the estimated prevalence of children starting cART with severe immunodeficiency declined from 76% in 2004 to 63% in 2010. Corresponding figures for lower middle-income countries were from 77% to 66% and for upper middle-income countries from 75% to 58%. In the United States, the percentage decreased from 42% to 19% during the period 1996 to 2006. In low- and middle-income countries, infants and children aged 12-15 years had the highest prevalence of severe immunodeficiency at cART initiation.
Conclusions: Despite progress in most low- and middle-income countries, many children continue to start cART with severe immunodeficiency. Early diagnosis and treatment of HIV-infected children to prevent morbidity and mortality associated with immunodeficiency must remain a global public health priority.

Abstract access

Editor's notes: This article describes trends and determinants of CD4 cell measures at antiretroviral therapy (ART) initiation in about 35,000 children in low, middle, and high-income countries. Temporal trends in CD4 measures at ART initiation are a useful indicator of the health system's ability to identify and treat eligible children in a timely fashion. They are also a useful measure of responsiveness to guideline changes.

Previous WHO guidelines recommended early ART initiation, regardless of immunologic or clinical thresholds. But the authors found that in 2010, approximately two-thirds of children below two years of age, in low- and middle-income countries were still starting ART with severe immunodeficiency.

Delayed country-level implementation of WHO guidelines, poor access to early infant diagnosis, slow turn-around time of test results, and limited ART availability for infants and young children are all contributing factors to this delayed ART initiation. The authors point out that timely diagnosis of paediatric HIV does not necessarily result in timely ART. The main reasons for this diagnosis to treatment gap include HIV diagnostic tests and paediatric ART being located at separate sites without robust referral mechanisms between services. There are challenges with CD4 measurement to determine eligibility. These include access to tests, turn-around time and interpretation of results and health care worker discomfort with treating children.

Currently, only 22% of children living with HIV in sub-Saharan Africa are receiving ART. To decrease the treatment gap among children, WHO 2013 guidelines recommend universal ART for all children living with HIV, aged below five years of age, irrespective of CD4 count or clinical stage. Removing the requirement for a CD4 measurement also removes the time lag while waiting for CD4 results. Thus the guidelines aim both to increase treatment accessibility and to accelerate treatment initiation for all children.

Implementation of routine counselor-initiated opt-out HIV testing on the adult medical ward at Kamuzu Central Hospital, Lilongwe, Malawi.


The optimal approach of provider-initiated HIV testing and counseling (PITC) for inpatients in high-burden settings is unknown. We prospectively evaluated the implementation of task-shifting from clinician-referral to counselor-initiated PITC on the medical wards of Kamuzu Central Hospital, Malawi. The majority of patients (1905/3154, 60.4%) had an unknown admission HIV status. Counselors offered testing to 66.6% (1268/1905). HIV prevalence was 39.3%. Counselor-initiated PITC significantly increased HIV testing by 85% (643/2957 vs. 1268/3154), resulting in an almost 2-fold increase in patients with known HIV status (2447/3154 vs. 1249/3154) (both p<.0001), with 17.9% of those tested receiving a new diagnosis of HIV.

Abstract access
Editor’s notes: UNAIDS estimates that in sub-Saharan Africa more than half of all people living with HIV remain unaware of their status and thus have no opportunity to access HIV care. Provider-initiated testing and counselling has been successful in increasing coverage of HIV testing in antenatal and tuberculosis clinics. In in-patient settings, it is most often the responsibility of a clinician to initiate the offer of HIV testing. Even when the universal offer of HIV testing is policy, many people may be missed.

In this study from a tertiary referral hospital in Malawi, counsellors were given responsibility for offering testing to all in-patients in the short-stay and medical wards. Prior to this programme, only 22% of people in these wards had an HIV test, and 31% of people tested were HIV-positive. During the programme period, some 60% of people admitted had unknown HIV status, of whom 67% were tested by counsellors. The refusal rate was very low, 3.2%. Some 39% of people tested were HIV positive. This seems a very effective way to maximise the number of medical in-patients who know their HIV status, thus allowing people to access appropriate care. Similar task-shifting activities have been undertaken to identify in-patients who are coughing and to ensure that their sputum is tested for tuberculosis. In settings where both HIV and tuberculosis are common, a programme combining counsellor-initiated HIV testing and cough screening could maximise case finding for both diseases. This would enable earlier initiation of treatment and reduce the risk of nosocomial transmission of tuberculosis.

3. Avoid TB deaths

CD4 deficit and tuberculosis risk persist with delayed antiretroviral therapy: 5-year data from CIPRA HT-001.


Setting: Port-au-Prince, Haiti.

Objective: To determine long-term effects of early vs. delayed initiation of antiretroviral therapy (ART) on immune recovery and tuberculosis (TB) risk in human immunodeficiency virus (HIV) infected individuals.

Design: Open-label randomized controlled trial of immediate ART in HIV-infected adults with CD4 counts between 200 and 350 cells/mm³ vs. deferring ART until the CD4 count was <200 cells/mm³. The primary comparisons were CD4 counts over time and risk for incident TB, with 5 years of follow-up.

Results: A total of 816 participants were enrolled, with 408 in each treatment arm. The early treatment group started ART within 2 weeks, while the deferred treatment group started ART a median of 1.3 years after enrollment. After 5 years, the mean CD4 count in the early treatment group was significantly higher than in the deferred treatment group (496 cells/mm³, 95% confidence interval [CI] 477-515 vs. 373 cells/mm³, 95%CI 357-389; P < 0.0001). TB risk was higher in the deferred treatment group (unadjusted HR 2.41, 95%CI 1.56-3.74; P < 0.0001) and strongly correlated with lower CD4 counts in time-dependent multivariate analysis.

Conclusion: Delays in ART initiation for HIV-infected adults with CD4 counts of 200-350 cells/mm³ can result in long-term immune dysfunction and persistent increased risk for TB.
Editor's notes: There is a solid evidence base to support the initiation of antiretroviral therapy (ART) for adults living with HIV with CD4+ cell count ≤350 cells/µL. One randomised controlled trial in Haiti (CIPRA HT-001) demonstrated a 75% reduction in mortality with initiation of ART at CD4+ cell count 200-350 cells/µL compared to deferring until CD4+ cell count was <200 cells/µL. That same trial demonstrated a 50% reduction in incident TB disease with early ART, over three years of follow-up.

This paper presents a subsequent analysis from this trial with extended follow-up to five years. This analysis reports on whether or not the effect of early ART was maintained, and the long-term effect on CD4+ recovery. The beneficial impact of early ART on incident TB disease was indeed maintained over the five years of follow-up. Half of the TB cases in the deferred ART group occurred before the initiation of ART but the differential risk persisted beyond the initiation of ART.

There was also a clear benefit of early ART on immune recovery. More than 75% of participants in the early ART group achieved a CD4+ cell count >500 cells/µL by five years, compared to fewer than 25% of people in the deferred ART group. The effect of early ART on incident TB was only partially modified after adjustment for time-updated CD4+ cell count, suggesting that early ART has benefit over and above its effect on CD4+ cell count recovery.

Although this is clear evidence to start ART promptly in people with severe immunosuppression, these data do not address the question of whether ART at CD4+ cell counts above 350 cells/µL influences the risk of TB disease, and this information is eagerly awaited from ongoing clinical trials.

4. Eliminate stigma and discrimination

Domestic violence among adolescents in HIV prevention research in Tanzania: participant experiences and measurement issues.


Under-representation of female adolescents in HIV clinical trials may inhibit their access to future prevention technologies. Domestic violence, broadly defined as violence perpetrated by intimate partners and/or family members, may affect trial participation. This study describes violence in the lives of adolescents and young women in Tanzania, explores use of the Women's Experience with Battering (WEB) Scale to measure battering, and examines the associations between battering and socio-demographic and HIV risk factors. Community formative research (CFR) and a mock clinical trial (MCT) were conducted to examine the challenges of recruiting younger (15-17) versus older (18-21) participants into HIV prevention trials. The CFR included qualitative interviews with 23 participants and there were 135 MCT participants. The WEB was administered in both the CFR and MCT.

Nineteen CFR participants experienced physical and/or sexual violence and 17 % scored positive for battering. All married participants reported partner-related domestic violence, and half scored positive for battering. Many believed beatings were normal. None of the single participants scored positive on battering, but one-third reported abuse by relatives. Among MCT participants, 15 % scored positive for battering; most perpetrators were relatives. Younger participants were more likely to report battering. Adolescents experienced high rates of domestic violence and the WEB captured battering from both partners and relatives. The level of familial violence was unexpected and has implications for parental roles in study recruitment. Addressing adolescent abuse in HIV prevention trials and in the general population should be a public health priority.

Abstract access
**Editor’s notes:** Despite their heightened HIV vulnerability, adolescent girls are under-represented in clinical trials on HIV prevention technologies. Domestic violence is a known HIV risk factor for adolescent girls and the authors posit that it may also be a barrier to their participation in clinical trials. This lack of participation may in turn inhibit their access to future prevention technologies. This paper contributes both methodological insights about the measures that can be applied in low-income settings to screen for domestic violence and substantive evidence about the high rates of familial as well as partner associated violence and battering among this group.

The paper draws on data from a larger study conducted in the United Republic of Tanzania which examined recruitment and retention of adolescent girls, aged 15-21 years, in HIV prevention trials. The paper examines the prevalence and type of domestic violence among this group and the capacity of the Women’s Experience with Battering (WEB) scale to measure this. Although the WEB scale has not been used in low income countries before, the authors report that it may have considerable value in identifying exposure to domestic violence and battering among trial participants. Certain adaptations may be necessary, to identify women who are subject to violence and battering but do no report being afraid of the perpetrator. The qualitative study component suggests that this may reflect how beatings are considered a normal aspect of intimate and familial relations. Although this assessment tool is likely to be able to inform trial retention initiatives, the adolescent girls need to be able to participate in these trials. So the use of the scale appears to be limited in its contribution to improving initial recruitment into trials.

The levels of familial battering were higher than expected. This is likely to have implications for parental roles in research and contributes to the ethical concerns of relying on parental consent in HIV prevention trials rather than pursuing the route of autonomy in consenting. This is illustrated by the study itself requiring parental consent for girls aged 15 years. This paper’s focus was on how to address the under-representation of adolescent girls in HIV prevention trials. Further, it provides valuable evidence on the high rates of exposure of adolescent girls to domestic violence from partners and their relatives. This evidence contributes to the call for greater attention to adolescent domestic violence in global health.

**Predictors of internalised HIV-related stigma: a systematic review of studies in sub-Saharan Africa.**


Objective: This systematic review aims to synthesize evidence on predictors of internalised HIV stigma amongst people living with HIV in sub-Saharan Africa.

Method: PRISMA guidelines were used. Studies were identified through electronic databases, grey literature, reference harvesting and contacts with key researchers. Quality of findings was assessed through an adapted version of the Cambridge Quality Checklists.

Results: A total of 590 potentially relevant titles were identified. Seventeen peer-reviewed articles and one draft book chapter were included. Studies investigated socio-demographic, HIV-related, intra-personal and inter-personal correlates of internalised stigma. Eleven articles used cross-sectional data, six articles used prospective cohort data and one used both prospective cohort and cross-sectional data to assess correlates of internalised stigma. Poor HIV-related health weakly predicted increases in internalized HIV stigma in three longitudinal studies. Lower depression scores and improvements in overall mental health predicted reductions in
Internalized HIV stigma in two longitudinal studies, with moderate and weak effects respectively. No other consistent predictors were found.

Conclusion: Studies utilizing analysis of change and accounting for confounding factors are necessary to guide policy and programming but are scarce. High-risk populations, other stigma markers that might layer upon internalised stigma, and structural drivers of internalised stigma need to be examined.

Abstract access

Editor’s notes: Internalized stigma can act as a barrier to HIV prevention and treatment. It can occur when a person living with HIV endorses negative attitudes associated with HIV and accepts these attitudes as applicable to themselves. Few stigma reduction programmes exist for people living with HIV. However, two recent studies have illustrated that internalized stigma reduction may be feasible through programmes targeting individual level factors. This paper systematically reviewed the evidence on predictors of internalized stigma among people living with HIV. The review included 18 papers looking at 13 unique studies in South Africa, Lesotho, Malawi, United Republic of Tanzania, Swaziland, Mozambique, Uganda, Kenya and Burkina Faso. All included studies were observational including prospective cohort and cross-sectional study designs. In all studies, participants were recruited through health facilities. Most included studies did not report on sampling methods.

All included studies defined internalized stigma as a negative self-perception due to HIV status and the resultant feelings of shame, difficulties around disclosure and self-exclusion. Only one study looked at the effect of antiretroviral therapy (ART) use on internalized stigma and found no evidence of an association. There was weak evidence across three studies that improved physical health (measured as improved physical functioning and fewer HIV-associated symptoms) lead to reductions in internalized HIV stigma. Two studies found some evidence that lower depression scores and improvements in overall mental health predicted reductions in internalized HIV stigma. There were inconsistent findings on whether time on ART had any association with internalized stigma. No other associations with socio-demographic or interpersonal factors were found. This is a field of new and emerging research and no implications for practice can be drawn given the inconsistent findings across studies. The cross-sectional nature of most of the included studies means that it is not possible to assess long-term associations. Further research is needed to understand the factors associated with internalized stigma and how these might change over time. Future research should use rigorous study methods and should focus on key populations, HIV transmission, and structural drivers of HIV.

5. Strengthening HIV integration

‘Deep down in their heart, they wish they could be given some incentives’: a qualitative study on the changing roles and relations of care among home-based caregivers in Zambia.


Background: Across sub-Saharan Africa, the roll-out of antiretroviral treatment (ART) has contributed to shifting HIV care towards management of a chronic health condition. While the balance of professional and lay tasks in HIV care-giving has been significantly altered due to changing skills requirements and task-shifting initiatives, little attention has been given to the effects of these changes on health workers’ motivation and existing care relations.
Methods: This paper draws on a cross-sectional, qualitative study that explored changes in home-based care (HBC) in the light of widespread ART rollout in the Lusaka and Kabwe districts of Zambia. Methods included observation of HBC daily activities, key informant interviews with programme staff from three local HBC organisations (n = 17) and ART clinic staff (n = 8), as well as in-depth interviews with home-based caregivers (n = 48) and HBC clients (n = 31).

Results: Since the roll-out of ART, home-based caregivers spend less time on hands-on physical care and support in the household, and are increasingly involved in specialised tasks supporting their clients’ access and adherence to ART. Despite their pride in gaining technical care skills, caregivers lament their lack of formal recognition through training, remuneration or mobility within the health system. Care relations within homes have also been altered as caregivers’ newly acquired functions of monitoring their clients while on ART are met with some ambivalence. Caregivers are under pressure to meet clients and their families’ demands, although they are no longer able to provide material support formerly associated with donor funding for HBC.

Conclusions: As their responsibilities and working environments are rapidly evolving, caregivers’ motivations are changing. It is essential to identify and address the growing tensions between an idealized rhetoric of altruistic volunteerism in home-based care, and the realities of lay worker deployment in HIV care interventions that not only shift tasks, but transform social and professional relations in ways that may profoundly influence caregivers’ motivation and quality of care.

Abstract Full-text [free] access

Editor’s notes: This paper fills an important gap. The authors examine the impact of the roll-out of antiretroviral treatment (ART) on home-based carers. Many papers have focused on recipients of ART and the effect on clinic services of providing ART. Little has been said about the impact of ART on home-based carers. Community health workers providing home-based care have been an important part of the support network for people living with HIV. It has been accepted that they provide the service as volunteers, and many have taken great pride in their work. The authors report a growing resentment at the lack of compensation for their work. Home-based carers have gained skills in supporting people on ART, acting as intermediaries between clinic and the person receiving care. Dwindling donor support for food and other items, provided to people living with HIV, has also affected home-based carers. They were often the ones who brought that aid to people living with HIV, and they are sometimes blamed for the loss. They may also be resented for checking up on ART adherence, affecting the trust between carer and the person living with HIV. This paper highlights the importance of looking at the unintended consequences of changes in healthcare delivery. A timely reminder that shifting treatment responsibilities away from the clinic is not without costs.