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

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UNAIDS
1. HIV testing and treatment

Effects of a multicomponent intervention to streamline initiation of antiretroviral therapy in Africa: a stepped-wedge cluster-randomised trial.


Background: In Africa, up to 30% of HIV-infected patients who are clinically eligible for antiretroviral therapy (ART) do not start timely treatment. We assessed the effects of an intervention targeting prevalent health systems barriers to ART initiation on timing and completeness of treatment initiation.

Methods: In this stepped-wedge, non-blinded, cluster-randomised controlled trial, 20 clinics in southwestern Uganda were randomly assigned in groups of five clinics every 6 months to the intervention by a computerised random number generator. This procedure continued until all clinics had crossed over from control (standard of care) to the intervention, which consisted of opinion-leader-led training and coaching of front-line health workers, a point-of-care CD4 cell count testing platform, a revised counselling approach without mandatory multiple pre-initiation sessions, and feedback to the facilities on their ART initiation rates and how they compared with other facilities. Treatment-naive, HIV-infected adults (aged ≥18 years) who were clinically eligible for ART during the study period were included in the study population. The primary outcome was ART initiation 14 days after first clinical eligibility for ART. This study is registered with ClinicalTrials.gov, number NCT01810289.

Findings: Between April 11, 2013, and Feb 2, 2015, 12 024 eligible patients visited one of the 20 participating clinics. Median CD4 count was 310 cells per µL (IQR 179-424). 3753 of 4747 patients (weighted proportion 80%) in the intervention group had started ART by 2 weeks after eligibility compared with 2585 of 7066 patients (38%) in the control group (risk difference 41.9%, 95% CI 40.1-43.8). Vital status was ascertained in a random sample of 208 patients in the intervention group and 199 patients in the control group. Four deaths (2%) occurred in the intervention group and five (3%) occurred in the control group.

Interpretation: A multicomponent intervention targeting health-care worker behaviour increased the probability of ART initiation 14 days after eligibility. This intervention consists of widely accessible components and has been tested in a real-world setting, and is therefore well positioned for use at scale.

Abstract access

Editor’s notes: As noted in another article in this month’s digest, early mortality remains high among people starting antiretroviral therapy (ART). People with advanced disease are at particularly high risk. Previous research has illustrated that mortality was even higher during the period between entering care and starting ART. ART start may be delayed for many reasons, some attributable to the person and others to the health system. Some of the health system delays date from practice early in ART roll-out. Great emphasis was placed on ART counselling, usually requiring people to attend several counselling sessions prior to initiating treatment, because of concerns about poor adherence. This practice has persisted despite evidence that treatment outcomes are no worse if ART is initiated rapidly with concurrent counselling rather than delaying ART initiation until after counselling has been completed.
In this study, the investigators tested a complex activity aiming to accelerate ART initiation in primary health care clinics in Uganda. This was developed based on health promotion literature, and was a combination of training led by opinion-leaders to counter the widespread belief that delays to ART initiation are not harmful. There was also a more flexible approach to ART counselling and the need for treatment supporters; introduction of point of care CD4 machines so that ART eligibility could be assessed in-session; and feedback to facilities concerning their performance compared to other clinics. The programme was successful in accelerating ART initiation. This approach holds promise as an effective method to implement change in health facilities. However, as more countries adopt the WHO guidance to offer ART regardless of CD4 count, the contribution of point of care CD4 machines in similar approaches may diminish. This is a common challenge for generalisability from randomised trials at a time of rapid policy changes. Cost and cost-effectiveness analyses will be reported later.

The study was not primarily designed to determine the effect of the activity on patient-relevant outcomes, which were measured in a small subset of people, and illustrated no difference in mortality after one year. Of note, mortality was very low in both groups (2% programme versus 3% control), which may be partly explained by the relatively high median CD4 count at enrolment, and around one-quarter of participants being pregnant women. It would be very interesting to see whether this programme has an effect on early mortality in settings and populations where early survival is less good.

Mortality in the first 3 months on antiretroviral therapy among HIV-positive adults in low- and middle-income countries: a meta-analysis.


Previous meta-analyses reported mortality estimates of 12-month post-antiretroviral therapy (ART) initiation; however, 40%-60% of deaths occur in the first 3 months on ART, a more sensitive measure of averted deaths through early ART initiation. To determine whether early mortality is dropping as treatment thresholds have increased, we reviewed studies of 3 months on ART initiation in low- to middle-income countries. Studies of 3-month mortality from January 2003 to April 2016 were searched in 5 databases. Articles were included that reported 3-month mortality from a low- to middle-income country; nontrial setting and participants were ≥15. We assessed overall mortality and stratified by year using random effects models. Among 58 included studies, although not significant, pooled estimates show a decline in mortality when comparing studies whose enrollment of patients ended before 2010 (7.0%; 95% CI: 6.0 to 8.0) with the studies during or after 2010 (4.0%; 95% CI: 3.0 to 5.0). To continue to reduce early HIV-related mortality at the population level, intensified efforts to increase demand for ART through active testing and facilitated referral should be a priority. Continued financial investments by multinational partners and the implementation of creative interventions to mitigate multidimensional complex barriers of accessing care and treatment for HIV are needed.

Abstract access

Editor’s notes: Early mortality among people initiating antiretroviral therapy (ART) remains high, presumed to be because many people living with HIV present when already very sick with advanced HIV disease. This systematic review included 43 studies from Africa and 13 from Asia. Its main aim was to see whether the evolution of guidelines recommending ART initiation at progressively higher CD4 counts over this period had reduced early mortality (defined as death within three months of ART start) and, by implication, the proportion of people starting ART who had advanced disease. To
investigate this, the authors compared studies where enrolment ended before 2010 with studies that had started later.

Overall early mortality was six percent. Because of the large numbers lost to follow up this will be an underestimate. The authors attempted to compensate for this, and calculated an adjusted overall figure of more than 10%. There was a fall in early mortality from seven percent to four percent (unadjusted) between the early and late periods but although the trend was consistent the difference was not significant.

In only four of the 58 studies was the median CD4 count at ART initiation above 200x10^6/l. It seems likely that even when policies to initiate ART at high CD4 counts are adopted, additional efforts will be necessary to promote initiation of ART and retention in care for people who feel well. This is in order to reduce the number of people starting ART with advanced disease and consequently at very high risk of early death.

Weekends-off efavirenz-based antiretroviral therapy in HIV-infected children, adolescents, and young adults (BREATHER): a randomised, open-label, non-inferiority, phase 2/3 trial.


Background: For HIV-1-infected young people facing lifelong antiretroviral therapy (ART), short cycle therapy with long-acting drugs offers potential for drug-free weekends, less toxicity, and better quality-of-life. We aimed to compare short cycle therapy (5 days on, 2 days off ART) versus continuous therapy (continuous ART).

Methods: In this open-label, non-inferiority trial (BREATHER), eligible participants were aged 8-24 years, were stable on first-line efavirenz with two nucleoside reverse transcriptase inhibitors, and had HIV-1 RNA viral load less than 50 copies per mL for 12 months or longer. Patients were randomly assigned (1:1) to remain on continuous therapy or change to short cycle therapy according to a computer-generated randomisation list, with permuted blocks of varying size, stratified by age and African versus non-African sites; the list was prepared by the trial statistician and randomisation was done via a web service accessed by site clinician or one of the three coordinating trials units. The primary outcome was the proportion of participants with confirmed viral load 50 copies per mL or higher at any time up to the 48 week assessment, estimated with the Kaplan-Meier method. The trial was powered to exclude a non-inferiority margin of 12%. Analyses were intention to treat. The trial was registered with EudraCT, number 2009-012947-40, ISRCTN, number 97755073, and CTA, number 27505/0005/001-0001.

Findings: Between April 1, 2011, and June 28, 2013, 199 participants from 11 countries worldwide were randomly assigned, 99 to the short cycle therapy and 100 to continuous therapy, and were followed up until the last patient reached 48 weeks. 105 (53%) were men, median age was 14 years (IQR 12-18), and median CD4 cell count was 735 cells per µL (IQR 576-968). Six percent (6%) patients assigned to the short cycle therapy versus seven percent (7%) assigned to continuous therapy had confirmed viral load 50 copies per mL or higher (difference -1.2%, 90% CI -7.3 to 4.9, non-inferiority shown). 13 grade 3 or 4 events occurred in the short cycle therapy group and 14 in the continuous therapy group (p=0.89). Two ART-related adverse events (one gynaecomastia and one spontaneous abortion) occurred in the short cycle therapy group compared with 14 (p=0.02) in the continuous therapy group (five lipodystrophy, two gynaecomastia, one suicidal ideation, one dizziness, one headache and syncope, one spontaneous abortion, one neutropenia, and two raised transaminases).
Interpretation: **Non-inferiority of maintaining virological suppression in children, adolescents, and young adults was shown for short cycle therapy versus continuous therapy at 48 weeks, with similar resistance and a better safety profile.** This short cycle therapy strategy is a viable option for adherent HIV-infected young people who are stable on efavirenz-based ART.

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

**Editor’s notes:** Increasing number of children born with HIV infection, who would otherwise have died in infancy, are now reaching adolescence because of the scale-up of antiretroviral therapy (ART). Adherence to treatment for chronic illnesses often drops as children approach adolescence, and unfortunately HIV is no exception.

**BREATHER** is an open-label, non-inferiority trial comparing continuous daily ART (CT) with short cycle treatment (SCT) enabling two days off treatment every week. The participants were aged 8 to 24 years and had to have been virally suppressed for at least one year prior to enrolment on an ART regimen containing efavirenz. At 48 weeks, 6.1% of children in the SCT arm versus 7.3% in the CT arm had virologic rebound (defined as an HIV viral load > 50 copies/ml), demonstrating that SCT is non-inferior to CT. There was no statistical difference between arms in the proportion who developed major resistance mutations or in proportion of adverse events.

This is the first trial to demonstrate that controlled interruption appears to be safe in terms of maintaining viral suppression and lack of emergence of drug resistance mutations. Notably, the trial was conducted in geographically diverse settings (11 countries) and achieved an impressive retention rate with only one participant being lost to follow-up. In addition, the strategy was highly acceptable to participants, particularly as it provided a legitimate way of missing doses. Children are expected to take ART for 20 years longer on average than adults and strategies that enable time off ART may be an effective way to reduce treatment fatigue. In addition, reduced ART usage may provide potential cost savings.

A concern, however, is that such a strategy may give out the detrimental message that missing doses is acceptable and may not affect the viral load. Therefore, appropriate counselling is important to ensure that people understand that there is a maximum break in treatment of two designated days per week. It is also important to note that the findings of this study are only generalisable to people who are stable on ART, who have not experienced treatment failure and who are taking efavirenz-based regimens. The trial was carried out with intensive viral load monitoring and further research is required to work out how such a strategy could be safely implemented in settings where routine viral load monitoring may not be available.

Viral suppression is the ultimate goal to improve health outcomes and reduce HIV transmission. Consistent adherence to ART is critical to ensure sustained virologic suppression. Children and adolescents face multiple challenges to adhere to treatment and a number of different approaches to address this are required- this trial now provides an innovative and promising option to offer to children.

**Barriers and facilitators to interventions improving retention in HIV care: a qualitative evidence meta-synthesis.**


**Retention in HIV care is vital to the HIV care continuum.** The current review aimed to synthesize qualitative research to identify facilitators and barriers to HIV retention in care interventions. A
qualitative evidence meta-synthesis utilizing thematic analysis. Prospective review registration was made in PROSPERO and review procedures adhered to PRISMA guidelines. Nineteen databases were searched to identify qualitative research conducted with individuals living with HIV and their caregivers. Quality assessment was conducted using CASP and the certainty of the evidence was evaluated using CERQual. A total of 4419 citations were evaluated and 11 were included in the final meta-synthesis. Two studies were from high-income countries, 3 from middle-income countries, and 6 from low-income countries. A total of eight themes were identified as facilitators or barriers for retention in HIV care intervention: (1) stigma and discrimination, (2) fear of HIV status disclosure, (3) task shifting to lay health workers, (4) human resource and institutional challenges, (5) mobile health (mHealth), (6) family and friend support, (7) intensive case management, and, (8) relationships with caregivers. The current review suggests that task shifting interventions with lay health workers were feasible and acceptable. mHealth interventions and stigma reduction interventions appear to be promising interventions aimed at improving retention in HIV care. Future studies should focus on improving the evidence base for these interventions. Additional research is needed among women and adolescents who were under-represented in retention interventions.

Abstract access

Editor's notes: Retention in HIV care is defined as the continued engagement in health services from enrolment in care to discharge or death of an individual living with HIV. There is strong evidence for the clinical and public health benefits of early antiretroviral therapy initiation. Individuals retained in care have lower mortality and a higher likelihood of viral suppression. Universal test and treat strategies are dependent on successful retention in HIV care.

A qualitative evidence meta-synthesis utilising thematic analysis was conducted. Some 11 studies were ultimately included in the review. Task shifting to non-specialist community caregivers was the most common activity identified in the review. Other programmes included home-based care, case management, primary HIV medical care, counselling, and mHealth.

The findings of the meta-synthesis highlight eight themes that were identified as facilitators or barriers for retention in HIV care programmes. This offers important insights for improving retention in care. However, more research is necessary to understand the experience of important sub populations including pregnant women, children and adolescents and key populations including gay men and other men who have sex with men. The authors also emphasise the need for studies to provide particular emphasis on the perspectives of individuals living with HIV and providers involved in programme delivery. This, they argue, would greatly enhance subsequent implementation and development of tailored programmes to retain individuals living with HIV in care.

They are looking just the same: antiretroviral treatment as social danger in rural Malawi.


Research on the social impact of ART pivots on questions of individual adherence and community acceptability of treatment programmes. In this paper we examine unexpected and unintended consequences of the scale-up of treatment in rural Malawi, using a unique dataset of more than 150 observational journals from three sites, spanning 2010 to 2013, focusing on men’s everyday conversations. Through thematic content analysis, we explore the emerging perception that the widespread availability of ART constitutes a form of social danger, as treatment makes it difficult to tell who does or does not have AIDS. This ambiguity introduced through ART is
interpreted as putting individuals at risk, because it is no longer possible to tell who might be infected - indeed, the sick now look healthier and "plumper" than the well. This ambivalence over the social impact of ART co-exists with individual demand for and appreciation of the benefits of treatment.

Abstract access

Editor’s notes: Widespread uptake of lifelong antiretroviral therapy means that our focus on its impact on communities should no longer be on its novelty but its consequences. This is a really interesting qualitative paper, which reflects on how men in a rural community in Malawi consider the social dangers that women who are on HIV treatment, specifically, pose to men. Through the content analysis of journal entries, which captured men’s informal conversations, the researchers draw out this sub group’s ambivalence towards antiretroviral therapy. Women who have HIV can become appealing sexual partners through projecting a healthy attractiveness. Thus treatment is portrayed as disruptive by putting men, attracted to plump/ healthy women, at risk. It is revealing that two of the key tenets of current prevention policy are relatively silent within these findings. Neither the message of the prevention benefits of treatment, in which people successfully adhering to treatment pose a minimal transmission risk, nor the message that sex should be protected, because anyone’s status should be considered unknown, appears to have a significant influence on either discourse or practice. By paying attention to the ‘hum’ and ‘chatter’ of everyday life we can learn about how treatment opportunities are interpreted. We can also gain insights into how they are understood in accordance with concerns around sexual opportunities and sexual appeal. These may change but they continue to be heavily shaped by gender.

2. Elimination of childhood infections

Suboptimal viral suppression rates among HIV-infected children in low- and middle-income countries: a meta-analysis.


Background: The 90-90-90 goals aim to achieve viral suppression in 90% of all HIV-infected people on antiretroviral treatment (ART), which is especially challenging in children. Global estimates of viral suppression among children in low- and middle-income countries (LMIC) are lacking. This study summarizes viral suppression rates in children on first-line ART in LMIC since the year 2000.

Methods: We searched for randomized controlled trials and observational studies and analyzed viral suppression rates among children started on ART during three time periods, based on major World Health Organization (WHO) guideline changes: early (2000-2005), intermediate (2006-2009), and current (2010 and later), using random effects meta-analysis.

Results: Seventy-two studies, reporting on 51,347 children and adolescents (<18 years), were included. After 12 months on first-line ART, viral suppression was achieved by 64.7% (95%CI 57.5-71.8) in the early, 74.2% (95%CI 70.2-78.2) in the intermediate, and 72.7% (95% 62.6-82.8) in the current time period. Rates were similar after 6 and 24 months of ART. Using an intention-to-treat analysis, 42.7% (95%CI 33.7-51.7) in the early, 45.7% (95%CI 33.2-58.3) in the intermediate, and 62.5% (95%CI 53.3-72.6) in the current period were suppressed. Long-term follow-up data were scarce.
Conclusion: Viral suppression rates among children on ART in LMIC were low and were considerably poorer than those previously found in adults in LMIC and children in high-income countries. Little progress has been made in improving viral suppression rates over the past years. Without increased efforts to improve pediatric HIV treatment, the 90-90-90 targets for children in LMIC will not be reached.

Abstract access

Editor’s notes: The authors have undertaken one of the largest meta-analyses to date of viral suppression rates among children and adolescents on first-line ART in low- and middle-income countries (LMIC). The same research group had previously conducted a meta-analysis among adults in LMIC using the same methodology. In this study, they found that viral suppression rates in children in LMIC are well below those previously found in adults in LMIC. The authors had planned to analyse viral suppression rates up to five years after initiation of first-line ART but found very few data on virologic outcomes after more than two years of follow-up.

The paucity of data on long-term outcomes in children highlights that children have been left behind compared to adults with respect to effective ART delivery. Systems to improve retention in care and adherence to treatment for children are urgently needed.

3. Key populations

Prevalence of HIV, HBV and HCV among street and labour children in Tehran, Iran.


Objectives: The existence of street and working children in Iran is undeniable. The precarious conditions of these children (including disrupted family, poverty, high prevalence of crime among relatives, family members and peers) cause social harm and high-risk behaviours, including drug addiction, selling sex or having sex with adolescents or peers. Here we explore the HIV, hepatitis B and hepatitis C status of street and working children in Tehran.

Methods: One thousand street and labour children, aged 10-18 years, were recruited by using the time-location sampling method, and semistructured questionnaires were used to find demographic information and information on HIV/AIDS-related high-risk sexual behaviours. Blood samples were collected from children, with use of the dried blood sampling method.

Results: 4.5% of children were HIV infected, 1.7% were infected with hepatitis B virus and 2.6% were infected with hepatitis C virus (HCV). Having parents who used drug, infected with HCV and having experience in trading sex significantly increased the likelihood of getting HIV among the street children of Tehran.

Conclusion: HIV prevalence among street children is much higher than general population (<0.1%), and in fact, the rate of positivity comes close to that among female sex workers in Iran. These findings must be an alarm for HIV policymakers to consider immediate and special interventions for this at-risk group.

Abstract access
Editor’s notes: Relatively few studies have been published on the prevalence of HIV and other communicable diseases in vulnerable populations in Iran. This paper presents results from a prevalence study among street children in Tehran, Iran. Researchers were able to survey 1000 street children, and children exploited by labour between the ages of 10-18, finding an HIV prevalence of 4.5%. The survey data revealed high rates of physical abuse, drug use, and school dropout, but it is not clear whether any of the children were already aware of their HIV status, or how many had acquired HIV perinatally. These important findings point to the imperative for programmes to address the needs of street children in Tehran, and additional research in other areas within the country where similar issues may be prevalent.


Background: HIV incidence in men who have sex with men (MSM) in the UK has remained unchanged over the past decade despite increases in HIV testing and antiretroviral therapy (ART) coverage. In this study, we examine trends in sexual behaviours and HIV testing in MSM and explore the risk of transmitting and acquiring HIV.

Methods: In this serial cross-sectional study, we obtained data from ten cross-sectional surveys done between 2000 and 2013, consisting of anonymous self-administered questionnaires and oral HIV antibody testing in MSM recruited in gay social venues in London, UK. Data were collected between October and January for all survey years up to 2008 and between February and August thereafter. All men older than 16 years were eligible to take part and fieldworkers attempted to approach all MSM in each venue and recorded refusal rates. Data were collected on demographic and sexual behavioural characteristics. We analysed trends over time using linear, logistic, and quantile regression.

Findings: Of 13 861 questionnaires collected between 2000 and 2013, we excluded 1985 (124 had completed the survey previously or were heterosexual reporting no anal intercourse in the past year, and 1861 did not provide samples for antibody testing). Of the 11 876 eligible MSM recruited, 1512 (13%) were HIV positive, with no significant trend in HIV positivity over time. 35% (531 of 1505) of HIV-positive MSM had undiagnosed infection, which decreased non-linearly over time from 34% (45 of 131) to 24% (25 of 106; p=0.01), while recent HIV testing (ie, in the past year) increased from 26% (263 of 997) to 60% (467 of 777; p<0.0001). The increase in recent testing in undiagnosed men (from 29% to 67%, p<0.0001) and HIV-negative men (from 26% to 62%, p<0.0001) suggests that undiagnosed infection might increasingly be recently acquired infection. The proportion of MSM reporting unprotected anal intercourse (UAI) in the past year increased from 43% (513 of 1187) to 53% (394 of 749; p<0.0001) and serosorting (exclusively) increased from 18% (207 of 1132) to 28% (177 of 6369; p<0.0001). 268 (2%) of 11 570 participants had undiagnosed HIV and reported UAI in the past year were at risk of transmitting HIV. Additionally 259 (2%) had diagnosed infection and reported UAI and non-exclusive serosorting in the past year. Although we did not collect data on antiretroviral therapy or viral load, surveillance data suggests that a small proportion of men with diagnosed infection will have detectable viral load and hence might also be at risk of transmitting HIV. 2633 (25%) of 10 364 participants were at high risk of acquiring HIV (defined as HIV-negative MSM either reporting one or more casual UAI partners in the past year or not exclusively serosorting). The proportions of MSM at risk of transmission or acquisition changed little over time (p=0.96 for MSM potentially at risk of transmission and p=0.275 for MSM at high risk of...
acquiring HIV). **Undiagnosed men reporting UAI and diagnosed men not exclusively serosorting had consistently higher partner numbers than did other MSM** over the period (median ranged from one to three across surveys in undiagnosed men reporting UAI, two to ten in diagnosed men not exclusively serosorting, and none to two in other men).

**Interpretation:** An increasing proportion of undiagnosed HIV infections in MSM in London might have been recently acquired, which is when people are likely to be most infectious. High UAI partner numbers of MSM at risk of transmitting HIV and the absence of a significant decrease in the proportion of men at high risk of acquiring the infection might explain the sustained HIV incidence. Implementation of combination prevention interventions comprising both behavioural and biological interventions to reduce community-wide risk is crucial to move towards eradication of HIV.

**Abstract access**

**Editor’s notes:** Despite wide-scale ART coverage, HIV incidence among gay men and other men who have sex with men remains high in many high-income countries, and is increasing in some locations. Although expanded testing and treatment are expected to lower HIV incidence, there are concerns that changes in risk behaviour may offset the impact of ART on HIV transmission. In this paper, the authors illustrate that among gay men and other men who have sex with men in London, the proportion who had tested for HIV in the past year increased considerably over the period 2000 and 2013, with a corresponding decrease in the numbers with undiagnosed HIV. However, there were increasing rates of condomless anal intercourse in both HIV-negative and HIV-positive men. Furthermore, men living with HIV who were undiagnosed, and men who were not exclusively serosorting (having sex with partners of the presumed same HIV status), reported increased numbers of sexual partners over the period of the surveys. Despite the increases in recent HIV testing, three percent of men in 2013 incorrectly perceived themselves to be HIV negative. This suggests that many men who are undiagnosed may be recent infections, so could be at high risk of transmission. Previous modelling studies have illustrated that increased sexual risk behaviour, particular among people who are unaware that they are HIV positive, could account for the observed increase in incidence in gay men and other men who have sex with men. The findings of this study demonstrate the importance of core groups to the continued transmission of HIV. Test and treat programmes alone may not be sufficient to reduce HIV incidence in gay men and other men who have sex with men populations. There is the need for appropriately tailored combination prevention programmes in order to make real gains against HIV among gay men and other men who have sex with men.

### 4. Elimination of gender inequalities

**Physical and sexual violence predictors: 20 years of the women’s interagency HIV study cohort.**


**Introduction:** Gender-based violence (GBV) threatens women’s health and safety. Few prospective studies examine physical and sexual violence predictors. **Baseline/index GBV history and polyvictimization** (intimate partner violence, non-partner sexual assault, and childhood sexual abuse) were characterized. Predictors of physical and sexual violence were evaluated over follow-up.
Methods: HIV-infected and uninfected participants (n=2838) in the Women's Interagency HIV Study provided GBV history; 2669 participants contributed 26 363 person years of follow-up from 1994 to 2014. In 2015-2016, multivariate log-binomial/Poisson regression models examined violence predictors, including GBV history, substance use, HIV status, and transactional sex.

Results: Overall, 61% reported index GBV history; over follow-up, 10% reported sexual and 21% reported physical violence. Having experienced all three forms of past GBV posed the greatest risk (adjusted incidence rate ratio [AIRR]physical=2.23, 95% CI=1.57, 3.19; AIRRsexual=3.17, 95% CI=1.89, 5.31). Time-varying risk factors included recent transactional sex (AIRRphysical=1.29, 95% CI=1.03, 1.61; AIRRsexual=2.98, 95% CI=2.12, 4.19), low income (AIRRphysical=1.22, 95% CI=1.01, 1.45; AIRRsexual=1.38, 95% CI=1.03, 1.85), and marijuana use (AIRRphysical=1.43, 95% CI=1.22, 1.68; AIRRsexual=1.57, 95% CI=1.19, 2.08). For physical violence, time-varying risk factors additionally included housing instability (AIRR=1.37, 95% CI=1.15, 1.62); unemployment (AIRR=1.38, 95% CI=1.14, 1.67); exceeding seven drinks/week (AIRR=1.44, 95% CI=1.21, 1.71); and use of crack, cocaine, or heroin (AIRR=1.76, 95% CI=1.46, 2.11).

Conclusions: Urban women living with HIV and their uninfected counterparts face sustained GBV risk. Past experiences of violence create sustained risk. Trauma-informed care, and addressing polyvictimization, structural inequality, transactional sex, and substance use treatment, can improve women's safety.

Abstract access

Editor’s notes: Gender-based violence results in physical, sexual and mental health morbidities, including HIV risk behaviours and HIV infection. There is limited prospective research on risk factors for physical and sexual violence. This study characterised leading violence forms – that is, intimate partner violence, non-partner sexual assault and childhood sexual assault – among a cohort of low-income women living in six American cities, some of whom are living with HIV. It also examined predictors of violence experience during follow-up. This study found extensive gender-based violence of all types, listed above, among this cohort of 2838 HIV positive and HIV negative women. Lifetime gender-based violence history was highly prevalent among white women (72%), non-heterosexual women (74%), homeless / unstably housed women (80%) and among women with a sex work history (81%). Experience of different types of gender-based violence by baseline conferred significant risk for subsequent physical and sexual violence. HIV status did not confer risk for violence victimisation indicating that low-income women in this setting are at considerable risk for violence, regardless of their HIV status.

This study presents data from the largest ongoing prospective cohort study among American women living with HIV and includes a demographically matched HIV negative comparison group. The key limitation of this study was the non-probability sample, which limits generalisability of these results. The results are best generalised to urban American women in high-HIV prevalence settings. Additional cohort studies are necessary in other settings and contexts. However, the findings demonstrate the need to understand and address different forms of violence experienced by the same woman for violence prevention and health promotion. They support the USA 2015 National HIV/AIDS strategy recommendations to address violence and trauma for women both at risk for and living with HIV.

The association between HIV disclosure status and perceived barriers to care faced by women living with HIV in Latin America, China, central/eastern Europe, and western Europe/Canada.
Generally, women are less likely than men to disclose their HIV status. This analysis examined the relationship between HIV disclosure and (1) perceived barriers to care and (2) quality of life (QoL) for women with HIV. The ELLA (EpidemioLogical study to investigate the popuLation and disease characteristics, barriers to care, and quAlity of life for women living with HIV) study enrolled HIV-positive women aged ≥18 years. Women completed the 12-item Barriers to Care Scale (BACS) questionnaire. QoL was assessed using the Health Status Assessment. BACS and QoL were stratified by dichotomized HIV disclosure status (to anyone outside the healthcare system). Multilevel logistic regression analysis was used to identify factors associated with disclosure. Of 1945 patients enrolled from Latin America, China, central/eastern Europe, and western Europe/Canada between July 2012 and September 2013, 1929 were included in the analysis (disclosed, n = 1724; nondisclosed, n = 205). Overall, 55% of patients lived with a husband/partner, 53% were employed, and 88% were receiving antiretroviral therapy. Patients who were with a serodiscordant partner were more likely to disclose (p = 0.0003). China had a disproportionately higher percentage of participants who did not disclose at all (nearly 30% vs. <15% for other regions). Mean BACS severity scores for medical/psychological service barriers and most personal resource barriers were significantly lower for the disclosed group compared with the nondisclosed group (p ≤ 0.02 for all). Compared with the disclosed group, the nondisclosed group reported statistically significantly higher (p ≤ 0.03) BACS item severity scores for 8 of the 12 potential barriers to care. The disclosed group reported better QoL. Overall, HIV nondisclosure was associated with more severe barriers to accessing healthcare by women with HIV.

Abstract Full-text [free] access

**Editor’s notes:** This study drew women participants from Latin America, China, central and eastern Europe and from western Europe and Canada. China was the only Asian country included and no African countries were included. This is important background information since the first sentence of the abstract ‘women are less likely than men to disclose HIV status’ is less likely to be true for, for example, parts of Africa. The study did not include men. So, no comparison can therefore be made with men’s disclosure behaviour. Nevertheless, the paper draws on data from 27 countries. Most women in the study did have access to ‘efficacious, well-tolerated’ antiretroviral therapy. A number of women, most notably in China, did not disclose their HIV status outside the health care system. Many women disclosed their status to a limited extent (only to some family and close friends). Non-disclosure affected access to health care as well as more general support. This pattern of non- or limited disclosure and barriers to access to care is replicated in many other places. The findings in this paper point to the importance globally of tackling stigma and providing a supportive health care and social setting for people living with HIV, so they can benefit fully from the treatment and care that is available.

**Relationship power and sexual violence among HIV-positive women in rural Uganda.**


Gender-based power imbalances place women at significant risk for sexual violence, however, little research has examined this association among women living with HIV/AIDS. We performed a cross-sectional analysis of relationship power and sexual violence among HIV-positive
women on antiretroviral therapy in rural Uganda. Relationship power was measured using the Sexual Relationship Power Scale (SRPS), a validated measure consisting of two subscales: relationship control (RC) and decision-making dominance. We used multivariable logistic regression to test for associations between the SRPS and two dependent variables: recent forced sex and transactional sex. Higher relationship power (full SRPS) was associated with reduced odds of forced sex (AOR = 0.24; 95 % CI 0.07-0.80; p = 0.020). The association between higher relationship power and transactional sex was strong and in the expected direction, but not statistically significant (AOR = 0.47; 95 % CI 0.18-1.22; p = 0.119). Higher RC was associated with reduced odds of both forced sex (AOR = 0.18; 95 % CI 0.06-0.59; p < 0.01) and transactional sex (AOR = 0.38; 95 % CI 0.15-0.99; p = 0.048). Violence prevention interventions with HIV-positive women should consider approaches that increase women's power in their relationships.

Abstract access

Editor's notes: This paper addresses the lack of research into relationship power and sexual violence among women living with HIV. The authors report on analysis of data, collected as part of an ongoing prospective cohort study on HIV medication adherence (Uganda AIDS Rural Treatment Outcomes (UARTO) study). The authors examined the association between relationship power and forced and transactional sex, based on their hypothesis that higher relationship power would be protective against both.

Participants for the main study were recruited from the Mbarara Regional Referral Hospital Immune Suppression Syndrome (ISS) Clinic, and in August 2007, the survey was modified for this sub-study to include measures on relationship power, intimate partner violence, stigma, social support, health behaviours, and food security. For the survey, relationship power was measured using the Sexual Relationship Power Scale (SRPS), which contains two subscales: relationship control (RC) and decision-making dominance (DMD).

The authors found a strong protective effect of relationship power on recent experience of forced sex and transactional sex among the participants. They also found that the association between RC and transactional sex was consistent with the association between RC and forced sex, which they suggest reveals that transactional sex, for these women, is associated with male dominance and control. That is, HIV-positive women with low relationship power may be more likely to engage in transactional sex due to poverty and food insecurity rather than for empowering reasons associated with agency.

The authors conclude with a call to consider the multiplicity of issues that need to be addressed for women living with HIV, including access to HIV care and treatment, social support, stigma and discrimination, disclosure, poverty and food security, and skills to negotiate safer sex and resolve conflict. In relationship to violence prevention they argue that anti-violence programmes should be integrated within HIV healthcare services as well as addressing structural factors through economic empowerment and gender transformative programmes.

5. Financing


Background: Pre-exposure prophylaxis (PrEP) with tenofovir and emtricitabine prevents HIV infections among men who have sex with men (MSM). PrEP can be given on a daily or intermittent basis. Unfortunately, PrEP is not reimbursed in most European countries. Cost-effectiveness analyses of PrEP among MSM in Europe are absent but are key for decision makers to decide upon PrEP implementation.

Methods: We developed a deterministic mathematical model, calibrated to the well-defined Dutch HIV epidemic among MSM, to predict the effect and cost-effectiveness of PrEP. PrEP was targeted to 10% of highly sexually active Dutch MSM over the coming 40 years. Cost-effectiveness ratios were calculated to predict the cost-effectiveness of daily and on-demand PrEP. Cost-effectiveness ratios below euro20 000 were considered to be cost-effective in this analysis.

Findings: Within the context of a stable HIV epidemic, at 80% effectiveness and current PrEP pricing, PrEP can cost as much as euro11 000 (IQR 9400-14 100) per quality-adjusted life-year (QALY) gained when used daily, or as little as euro2000 (IQR 1300-3000) per QALY gained when used on demand. At 80% effectiveness, daily PrEP can be considered cost-saving if the price of PrEP is reduced by 70%, and on-demand PrEP can be considered cost-saving if the price is reduced by 30-40%.

Interpretation: PrEP for HIV prevention among MSM in the Netherlands is cost-effective. The use of PrEP is most cost-effective when the price of PrEP is reduced through on-demand use or through availability of generic PrEP, and can quickly be considered cost-saving.

Abstract access

Editor’s notes: Evidence surrounding the clinical effectiveness of pre-exposure prophylaxis to prevent HIV infection has been building for years (see HIV This Month January 2016 and February 2015). This article now adds to the evidence with indications that pre-exposure prophylaxis is also cost-effective in a European setting.

The authors use a deterministic mathematical model to represent the HIV epidemic in the Netherlands among gay men and other men who have sex with men. They estimate the cost and cost-effectiveness of two models of pre-exposure prophylaxis usage: a daily dosage, and an ‘on demand’ dosage. Their base case analysis found that both usage models fell under a willingness-to-pay ratio of €20 000 per QALY gained over a 40-year time horizon, although the ‘on demand’ model was least expensive at only €2000 (IQR 1300-3000) per QALY gained. The model reflected some uncertainty around the results. However, very few results from the sensitivity analysis indicated a cost-per-QALY ratio above €20 000. Several scenarios indicated that pre-exposure prophylaxis was cost-saving.

Pre-exposure prophylaxis was approved by the European Medicines Agency in July 2016, however it is currently not reimbursed by most European governments. This paper provides important evidence to make a case in favour of recommending reimbursement. Although the willingness-to-pay threshold used (€20 000/QALY) does not have any formal recognition in the Netherlands, several independent analyses soliciting the Dutch society’s value of a QALY reflect values much higher than this. As noted in the comment accompanying this paper (Niessen and Jaffar), the potential cost of implementing pre-exposure prophylaxis on a large-scale could be higher than current budgetary priorities allow. Still, this is an important study adding to the mounting evidence that countries should begin to consider how pre-exposure prophylaxis can be made available to people at highest risk of HIV infection.
6. Health systems and services

Cognitive behavioural therapy for adherence and depression in patients with HIV: a three-arm randomised controlled trial.


Background: Depression is highly prevalent in people with HIV and has consistently been associated with poor antiretroviral therapy (ART) adherence. Integrating cognitive behavioural therapy (CBT) for depression with adherence counselling using the Life-Steps approach (CBT-AD) has an emerging evidence base. The aim of this study was to test the efficacy of CBT-AD.

Methods: In this three-arm randomised controlled trial in HIV-positive adults with depression, we compared CBT-AD with information and supportive psychotherapy plus adherence counselling using the Life-Steps approach (ISP-AD), and with enhanced treatment as usual (ETAU) including Life-Steps adherence counselling only. Participants were recruited from three sites in New England, USA (two hospital settings and one community health centre). Patients were randomly assigned (2:2:1) to receive CBT-AD (one Life-Steps session plus 11 weekly integrated sessions lasting up to 1 h each), ISP-AD (one Life-Steps session plus 11 weekly integrated sessions lasting up to 1 h each), or ETAU (one Life-Steps session and five assessment visits roughly every 2 weeks), randomisation was done with allocation software, in pairs, and stratified by three variables: study site, whether or not participants had been prescribed antidepressant medication, and whether or not participants had a history of injection drug use. The primary outcome was ART adherence at the end of treatment (4 month assessment) assessed via electronic pill caps (Medication Event Monitoring System [MEMS]) with correction for pocketed doses, analysed by intention to treat.

Findings: Patients were recruited from Feb 26, 2009, to June 21, 2012. Patients who were assigned to CBT-AD (94 randomly assigned, 83 completed assessment) had greater improvements in adherence (estimated difference 1.00 percentage point per visit, 95% CI 0.34 to 1.66, p=0.003) and depression (Center for Epidemiological Studies depression [CESD] score estimated difference -0.41, -0.66 to -0.16, p=0.001; Montgomery-Asberg depression rating scale [MADRS] score -4.69, -8.09 to -1.28, p=0.007; clinical global impression [CGI] score -0.66, -1.11 to -0.21, p=0.005) than did patients who had ETAU (49 assigned, 46 completed assessment) after treatment (4 months). No significant differences in adherence were noted between CBT-AD and ISP-AD (97 assigned, 87 completed assessment). No study-related adverse events were reported.

Interpretation: Integrating evidenced-based treatment for depression with evidenced-based adherence counselling is helpful for individuals living with HIV/AIDS and depression. Future efforts should examine how to best disseminate effective psychosocial depression treatments such as CBT-AD to people living with HIV/AIDS and examine the cost-effectiveness of such approaches.

Abstract access

Editor’s notes: Clinical depression is highly prevalent in people living with HIV, and common symptoms of depression (such as poor attention and negative thinking) can lead to poor adherence to ART. There is an emerging evidence base that integrating cognitive behaviour therapy (CBT) for adherence with CBT for depression may improve ART adherence, but this is based on relatively few, small, studies. This paper presents results of a full-scale three-arm efficacy trial to evaluate a CBT-based programme on HIV outcomes among people living with HIV with comorbid depression (CBT-
AD) compared with a time-matched information and supportive psychotherapy activity with adherence counselling (ISP-AD), and enhanced treatment as usual. The CBT-AD programme is based on the Life-Steps adherence counselling programme - a problem-solving approach to help people identify behavioural changes they can make to improve adherence. For both adherence (assessed using electronic pill caps) and depression, CBT-AD performed better than enhanced usual care over the four month treatment period and an eight month follow-up period, but was no better than ISP-AD. However, there was no effect on viral load or the proportion with detectable viral load, the end result of adherence. This may be because 90% of participants had viral suppression at baseline so there was a ceiling effect on improvement, because the increase in adherence may not have been sufficient to reach undetectable viral load or due to problems with measurement errors of adherence. This trial illustrates that psychosocial therapy for ART adherence has potential to improve adherence among people living with HIV. But further studies are necessary – including in LMIC, and restricting participants to people who are not virologically suppressed.


Background: The poor health of South Africans is known to be associated with a quadruple disease burden. In the second National Burden of Disease (NBD) study, we aimed to analyse cause of death data for 1997-2012 and develop national, population group, and provincial estimates of the levels and causes of mortality.

Method: We used underlying cause of death data from death notifications for 1997-2012 obtained from Statistics South Africa. These data were adjusted for completeness using indirect demographic techniques for adults and comparison with survey and census estimates for child mortality. A regression approach was used to estimate misclassified HIV/AIDS deaths and so-called garbage codes were proportionally redistributed by age, sex, and population group population group (black African, Indian or Asian descent, white [European descent], and coloured [of mixed ancestry according to the preceding categories]). Injury deaths were estimated from additional data sources. Age-standardised death rates were calculated with mid-year population estimates and the WHO age standard. Institute of Health Metrics and Evaluation Global Burden of Disease (IHME GBD) estimates for South Africa were obtained from the IHME GHDx website for comparison.

Findings: All-cause age-standardised death rates increased rapidly since 1997, peaked in 2006 and then declined, driven by changes in HIV/AIDS. Mortality from tuberculosis, non-communicable diseases, and injuries decreased slightly. In 2012, HIV/AIDS caused the most deaths (29.1%) followed by cerebrovascular disease (7.5%) and lower respiratory infections (4.9%). All-cause age-standardised death rates were 1.7 times higher in the province with the highest death rate compared to the province with the lowest death rate, 2.2 times higher in black Africans compared to whites, and 1.4 times higher in males compared with females. Comparison with the IHME GBD estimates for South Africa revealed substantial differences for estimated deaths from all causes, particularly HIV/AIDS and interpersonal violence.

Interpretation: This study related the reversal of HIV/AIDS, non-communicable disease, and injury mortality trends in South Africa during the study period. Mortality differentials show the importance of social determinants, raise concerns about the quality of health services, and provide
relevant information to policy makers for addressing inequalities. Differences between GBD estimates for South Africa and this study emphasise the need for more careful calibration of global models with local data.

Abstract Full-text [free] access

Editor’s notes: In South Africa in 2012, almost 500 people died every day from HIV or TB. One in every three deaths was associated with HIV or TB. Although these figures represent a substantial decline from the peak of the epidemic impact in 2006, they highlight the enormous challenge still facing this country.

South Africa is one of the few countries in Africa to have a robust civil registration system for deaths. However, there continue to be problems with misclassification of HIV-associated deaths. This analysis relied on somewhat complicated analytical methods to adjust mortality estimates. Only around half of those deaths ultimately defined as HIV associated had been originally coded as such in the registration system. The methods for adjustment differed from those used in the Global Burden of Disease (GBD) study. This explains the quite marked discrepancy in number of deaths attributed to HIV - this study estimated 40% fewer HIV-associated deaths than the GBD study.

This highlights that there is still quite a lot of uncertainty around cause-specific mortality estimates. So, although these data are useful to guide national and provincial priority setting, more fine-grain analysis is required to properly inform public health policies. There is a particular need to unpick the contribution of TB. In this respect, the recent announcement by the South African Department of Science of Technology to establish a network of health and demographic surveillance sites as a key component of the national research infrastructure is very welcome. With established verbal autopsy methods and innovations such as routine linkage to health service records, this will provide a framework to allow a deeper understanding of mortality.