UNAIDS Science now

HIV this month. Issue no. 6. June 2013

Welcome to the 6th issue of **HIV this month**! In this issue, we cover the following topics:

1. **Reduce sexual transmission**
   - Identifying hotspots of HIV infection in sub-Saharan Africa
   - High response rates to mobile phone surveys to monitor PrEP adherence and sexual behaviour
   - Need for focused HIV/STI interventions at informal drinking establishments in South Africa
   - Sexual transmission in St Petersburg may be self-sustaining without improved surveillance and prevention among partners of people who inject drugs
   - Low rates of HIV status disclosure amongst pregnant women in Morogoro, Tanzania
2. **Prevent HIV among drug users**
   - Extensive liver fibrosis in HIV-Hepatitis C co-infected patients compared to HCV mono-infected patients
3. **15 million accessing treatment**
   - Routine testing of paediatric hospital inpatients a critical entry point for identifying HIV positive children
   - High uptake of HIV testing and linkage to care using comprehensive community-based monitoring
   - Increased risk of mortality associated with delayed initiation of ART
   - Late diagnosis contributes to persistently high HIV-associated mortality in the United Kingdom
   - Multi-faceted community-based intervention for improving retention in care
   - High CD4 count on initiating ART associated with unstructured treatment interruptions
   - Preliminary evidence: tenofovir outperforms d4T and AZT in terms of the need for drug substitution and mortality outcomes
   - Children: higher rates of virological failure on nevirapine-, as compared to efavirenz-based ART
4. **Avoid TB deaths**
   - Dynamic model of active versus passive TB case finding
5. **Close the resource gap**
   - Aid disbursements to reproductive health stable or slightly increasing
   - New framework for delivering high-value care to patients with HIV/AIDS and co-occurring conditions
6. **Eliminate gender inequalities**
   - Intimate partner violence associated with poor ART adherence, disease progression and hospitalization
7. **Eliminate stigma and discrimination**

- Social support, safer sex lives and developing a post diagnosis identity

8. Strengthening HIV integration

- Integration of ANC and ART services increases PMTCT uptake but provision remains sub-optimal
- Almost a quarter of deaths in pregnant and post-partum women may be attributable to HIV
- Integrating HIV testing into routine infant immunization programmes
- Feasibility and acceptability of routine HIV testing into a general paediatric out-patient clinic

To find out how you can access a majority of scientific journals free of charge, check the ***UNAIDS Science now*** website by clicking here. If you would like to subscribe to ***HIV this month*** issues, click here. To unsubscribe, please click here. Please let us know what your interests are and what you think of ***HIV this month*** by sending us an email here. If you would like to recommend an article for inclusion, please contact us. Remember, a wealth of information on the HIV epidemic and responses to it are accessible at www.unaids.org.

Peter Godfrey-Faussett and Celeste Sandoval
UNAIDS

1. Reduce sexual transmission

Mapping HIV clustering: a strategy for identifying populations at high risk of HIV infection in sub-Saharan Africa.

Cuadros DF, Awad SF, Abu-Raddad LJ. Int J Health Geogr. 2013 May 22;12:28.

Background: The geographical structure of an epidemic is ultimately a consequence of the drivers of the epidemic and the population susceptible to the infection. The **'**know your epidemic**'** concept recognizes this geographical feature as a key element for identifying populations at higher risk of HIV infection where prevention interventions should be targeted. In an effort to clarify specific drivers of HIV transmission and identify priority populations for HIV prevention interventions, we conducted a **comprehensive mapping of the spatial distribution of HIV infection across sub-Saharan Africa** (SSA).

Methods: The main source of data for our study was the Demographic and Health Survey conducted in 20 countries from SSA. **We identified and compared spatial clusters with high and low numbers of HIV infections in each country** using Kulldorff spatial scan test. The test locates areas with higher and lower numbers of HIV infections than expected under spatial randomness. For each identified cluster, a likelihood ratio test was computed. A P-value was determined through Monte Carlo simulations to evaluate the statistical significance of each cluster.

Results: Our results suggest **stark geographic variations in HIV transmission patterns within and across countries of SSA**. About 14% of the population in SSA is located in areas of intense HIV epidemics. Meanwhile, another 16% of the population is located in areas of low HIV prevalence, where some behavioral or biological protective factors appear to have slowed HIV transmission.

Conclusions: Our study provides **direct evidence for strong geographic clustering of HIV infection across SSA**. This striking pattern of heterogeneity at the micro-geographical scale might reflect the fact that **most HIV epidemics in the general population in SSA are not far from their epidemic threshold. Our findings identify priority geographic areas for HIV programming, and support the need for spatially targeted interventions in order to maximize the impact on the epidemic in SSA.**

Abstract Full-text [free] access

***Editor's notes**: This novel study used DHS data to map the clustering of HIV at a local level in 20 sub-Saharan African countries. The method identifies 'hotspots' and 'cool spots' of HIV infection within each country, mapping the results in a visually striking way. The data show marked geographical variation within countries. For example, in Senegal, where overall prevalence is 0.75%, a hotspot with general population prevalence of 4.35% was identified. Conversely, within some countries with substantial HIV epidemics (Tanzania, Kenya, Malawi), the study identified settings with very low HIV prevalence. The authors present a 'relative risk' (ratio of HIV prevalence within the cluster to that outside the cluster) and, not surprisingly, find that this was higher in low prevalence countries. It may also be interesting to see an absolute risk, and estimated excess number of cases. The authors hypothesize that the spatial variation may be less to do with variation in behavioural and biological factors than to the fact that HIV infection transmission in SSA is close to the epidemic (or sustainability) threshold – which means that small changes in risk factors can generate substantial changes in HIV prevalence. The implication of this is that, by focusing on the HIV 'hotspots', even modest intervention-driven changes in risk behaviour may have considerable impact in reducing HIV prevalence.*

Daily short message service surveys to measure sexual behaviour and pre-exposure prophylaxis use among Kenyan men and women.

Curran K, Mugo NR, Kurth A, Ngure K, Heffron R, Donnell D, Celum C, Baeten JM. AIDS Behav. 2013 May 22. [Epub ahead of print]

Pre-exposure prophylaxis (PrEP) is a novel HIV prevention strategy which requires high adherence. **We tested the use of daily short message service (i.e., SMS/ text message) surveys to measure sexual behavior and PrEP adherence in Kenya**. Ninety-six HIV-uninfected adult individuals, taking daily oral PrEP in a clinical trial,

received daily SMS surveys for 60 days. **Most participants (96.9%) reported taking PrEP on ≥80% days**, but 69.8% missed at least one dose. Unprotected sex was reported on 4.9% of days; however, 47.9% of participants reported unprotected sex at least once. Unprotected sex was not correlated with PrEP use (OR=0.95). Participants reporting more sex were less likely to report PrEP non-adherence and those reporting no sex were most likely to report missing a PrEP dose (adjusted OR=1.87). **PrEP adherence was high, missed doses were correlated with sexual abstinence, and unprotected sex was not associated with decreased PrEP adherence.**

Abstract access

***Editor's notes**: This pilot study provides useful data both on self-reported adherence to PrEP, and sexual behaviour, among HIV-negative partners in serodiscordant partnerships, and on the potential for using mobile phones to collect potentially sensitive behaviour data. The study found high levels of self-reported adherence, especially related to greater sexual activity (but not with unprotected sex). Unprotected sex was reported more frequently by the SMS survey than in monthly clinic survey, which may reflect the daily data collection, and possibly lower social desirability bias provided by SMS. Questions about possible future sexual activity did not correlate well with reported activity, indicating that daily PrEP regimens may be better at providing optimal adherence than peri-coital regimens. For this pilot evaluation, the study population was select - participants in a clinical trial who had already received monthly counselling on risk behaviour and PrEP adherence, and restricted to those who already knew how to send and receive an SMS message, and who responded well to daily SMS surveys sent during a one-week run-in period. Previous studies of two-way SMS communication have shown more variable response rates, and it is likely that the high response, and adherence, seen here was partly due to the stringent selection criteria. However, the results illustrate the growing potential for using mobile phones for both data collection and adherence reminders.*

Bringing it home: community survey of HIV risks to primary sex partners of men and women in alcohol-serving establishments in Cape Town, South Africa.

Kalichman SC, Pitpitan E, Eaton L, Cain D, Carey KB, Carey MP, Harel O,Mehlomakhulu V, Simbayi LC, Mwaba K. Sex Transm Infect. 2013 May;89(3):231-6.Epub 2012 Dec 13.

Background: Concurrent sexual relationships facilitate the spread of HIV infection, and **sex with non-primary partners may pose particularly high risks for HIV transmission to primary partners.**

Objective: We examined the sexual and alcohol-related risks associated with sex partners outside of primary relationships among South African men and women in informal drinking establishments.

Methods: Men (n=4959) and women (n=2367) with primary sex partners residing in a Xhosa-speaking South African township completed anonymous surveys. Logistic regressions tested associations between having outside partners and risks for sexually transmitted infections (STI)/HIV.

Results: **Forty-four percent of men and 26% women with primary sex partners reported also having outside sex partners in the previous month**. Condom use with outside partners was inconsistent for men and women; **only 19% of men and 12% of women used condoms consistently with outside sex partners**. Multivariable regressions for men and women showed that having outside partners was significantly associated with having been diagnosed with an STI, consuming alcohol in greater frequency and quantity, alcohol use during sex, meeting sex partners in alcohol-serving venues, and higher rates of unprotected sex.

Conclusions: Having outside sex partners was associated with multiple risk factors for HIV infection among South African shebeen patrons**. Social and structural interventions that encourage condom use are needed for men and women with outside partners who patronise alcohol-serving venues.**

Abstract Full-text [free] access

***Editor's notes**: South Africa continues to have high HIV incidence, and this study focuses on a particularly high risk group – patrons of informal drinking venues. In this large survey, about half of men and a quarter of women with a regular partner reported having had an additional casual ('outside') partnership in the past month. Having*

outside partners was associated with multiple risk factors for HIV infection, including low levels of condom use. Despite limitations of self-reported data, these results highlight the high risk behaviour associated with attending informal drinking establishments, and the need to STI/HIV prevention interventions in these populations.

HIV transmission from drug injectors to partners who do not inject, and beyond: Modelling the potential for a generalised heterosexual epidemic in St Petersburg, Russia.

Mills HL, White E, Colijn C, Vickerman P, Heimer R. Drug Alcohol Depend. 2013 May 18. [Epub ahead of print]

Background: HIV infection is prevalent among drug injectors in St. Petersburg and their non-injecting heterosexual partners (PIDUs). **There are fears that sexual transmission of HIV from IDUs to PIDUs may portend a self-sustaining, heterosexual epidemic in Russia.**

Methods: Our model combines a network model of sexual partnerships of IDUs and non-IDUs to represent sexual transmission of HIV and a deterministic model for parenteral transmission among IDUs. Behavioural parameters were obtained from a survey of St. Petersburg IDUs and their sexual partners. We based our model fits on two scenarios for PIDU prevalence in 2006 (5.6% and 15.1%, calculated excluding and including HCV co-infected PIDUs respectively) and compared predictions for the general population HIV prevalence.

Results: Results indicate that **sexual transmission could sustain a non-IDU HIV epidemic**. The model indicates that general population prevalence may be greater than current estimates imply. Parenteral transmission drives the epidemic and **the PIDU bridge population plays a crucial role transferring infection to non-IDUs**. The model indicates that the high PIDU prevalence is improbable because of the high risk behaviour this implies; the lower prevalence is possible.

Conclusion: The model implies that t**ransmission through PIDUs will sustain a heterosexual epidemic, if prevalence among IDUs and PIDUs is as high as survey data suggest**. We postulate that current estimates of population prevalence underestimate the extent of the HIV epidemic because they are based on the number of registered cases only. Curtailing transmission among injectors and PIDUs will be vital in controlling heterosexual transmission.

Abstract access

***Editor's notes**: Current estimates of HIV prevalence both in the general population and in people who inject drugs in St Petersburg may under-estimate true prevalence due to imperfect methods of collecting surveillance data. The models in this study are based on a large respondent-driven sample of people who inject drugs, men who have sex with men, and their sexual partners. The results indicate that HIV prevalence in the general population may be at least twice as high as is higher than the current surveillance data imply, even under conservative assumptions. Furthermore, models that removed parenteral transmission from 2012 onwards (i.e. assuming 100% treatment strategy), the epidemic among people not injecting drugs would be sustained. These findings highlight the importance of improving surveillance and prevention activities in the bridging population in order to control the HIV epidemic, in addition to focusing on prevention and treatment of people who inject drugs.*

Predictors of HIV serostatus disclosure to partners among HIV-positive pregnant women in Morogoro, Tanzania.

Kiula ES, Damian DJ, Msuya SE. BMC Public Health. 2013 May 3;13(1):433. [Epub ahead of print]

Background: Prevention of mother to child transmission of HIV (PMTCT) has been scaled, to more than 90% of health facilities in Tanzania. Disclosure of HIV results to partners and their participation is encouraged in the program. This study aimed to determine the prevalence, patterns and predictors of HIV sero-status disclosure to partners among HIV positive pregnant women in Morogoro municipality, Tanzania.

Methods: A **cross sectional study** was conducted in March to May 2010 **among HIV-positive pregnant women who were attending for routine antenatal care in primary health care facilities** of the municipality and had been tested for HIV at least one month prior to the study. Questionnaires were used to collect information on possible predictors of HIV disclosure to partners.

Results: A total of 250 HIV-positive pregnant women were enrolled. **Forty one percent (102) had disclosed their HIV sero-status to their partners**. HIV-disclosure to partners was **more likely among pregnant women who were < 25 years old** [Adjusted odds ratio (AOR) = 2.2; 95% CI: 1.2--4.1], who **knew their HIV status before the current pregnancy** [AOR = 3.7; 95% CI: 1.7--8.3], and **discussed with their partner before testing** [AOR = 6.9; 95% CI: 2.4--20.1]. **Dependency on the partner for food/rent/school fees, led to lower odds of disclosure to partners** [AOR = 0.4; 95% CI: 0.1--0.7]. Nine out of ten women reported to have been counseled on importance of disclosure and partner participation.

Conclusions: Six in ten HIV positive pregnant women in this setting had not disclosed their results of the HIV test to their partners. **Empowering pregnant women to have an individualized HIV-disclosure plan, strengthening of the HIV provider initiated counseling and testing and addressing economic development**, may be some of the strategies in improving HIV disclosure and partner involvement in this setting.

Abstract Full-text [free] access

***Editor's notes**: Non-disclosure of HIV status to partners has implications not only for sexual transmission but also for the individual's ability to attend regularly for care, initiate treatment etc. This study showed that 41% of HIV positive pregnant women in Morogoro, Tanzania disclosed their HIV status to their partners and that 40% had not disclosed their status to anybody. Less than a fifth of women were accompanied by their partner when attending for antenatal care. The median time to disclosure from the time of diagnosis was 5 months. The authors highlight the fact that if the ambition of eliminating HIV infection in children is to be achieved, greater efforts on the benefits of disclosure and couples testing have to be undertaken. This study also found an association between financial dependency and non-disclosure of HIV status. The wider implications of this finding clearly extend beyond HIV care delivery. Follow-up data from this study on the association of HIV status disclosure and PMTCT related outcomes would be interesting.*

2. Prevent HIV among drug users

HIV, Age, and the Severity of Hepatitis C Virus–Related Liver Disease: A Cohort Study.

Kirk GD, Mehta SH, Astemborski J, Galai N, Washington J, Higgins Y, Balagopal A, Thomas DL. Ann Intern Med. 2013;158(9):658-666

Background**:** Persons with HIV infection have been reported to develop age-related diseases at younger ages than those without HIV. Whether this finding is related to HIV infection or failure to control for other risk factors is unknown.

Objective**: To investigate whether persons with HIV infection develop hepatitis C virus (HCV)–related liver disease at younger ages than similar persons without HIV.**

Design**: Comparison of the severity of liver fibrosis by age among persons who have HCV with and without HIV** followed concurrently in the same protocol.

Setting**: Observational cohort** from Baltimore, Maryland, participating in the ALIVE (AIDS Linked to the IntraVenous Experience) study.

Participants**: 1176 current and former injection drug users with antibodies to HCV.**

Measurements**: Liver fibrosis assessed semiannually from 2006 to 2011 by elastography** (FibroScan, Echosens, Paris, France) and using previously validated thresholds for clinically significant fibrosis and cirrhosis; concurrent assessment of medical history, alcohol and illicit drug use, HCV RNA levels, hepatitis B virus surface antigen level, body mass index, and (for those with HIV) $CD4^+$ lymphocyte count and HIV RNA levels.

Results**: Among 1176 participants with antibodies to HCV, the median age was 49 years and 34% were coinfected with HIV and HCV.** Participants contributed 5634 valid liver fibrosis measurements. **The prevalence of clinically significant fibrosis without cirrhosis (12.9% vs. 9.5%) and of cirrhosis (19.5% vs. 11.0%) was greater in persons coinfected with HIV and HCV than in those with only HCV (*P* < 0.001). Increasing age**

and HIV infection were independently associated with liver fibrosis, as were daily alcohol use, chronic hepatitis B virus infection, body mass index greater than 25 kg/m^2, and greater plasma HCV RNA levels. When these factors were kept constant**, persons with HIV had liver fibrosis measurements equal to those of persons without HIV, who were, on average, 9.2 years older.**

Limitation**:** The process of liver fibrosis began before the study in most persons.

Conclusion**:** In this cohort, **persons who have HCV with HIV have liver fibrosis stages similar to those without HIV who are nearly a decade older.**

Abstract access

Editor's notes*: Patients with HIV/HCV co-infection have markedly increased rates of liver disease, liver failure and death compared to patients with HCV mono-infection. Due to the shared routes of infection, HIV-infection is highly prevalent in individuals with HCV infection, and the co-infection rate of 34% seen in this study is typical of the reported US figures. Although ART has led to some improvement in outcomes, morbidity and mortality are still excessive in HIV/HCV co-infected patients. This is in part due to difficulties in initiating, adhering to, and managing the side effects of treatment, and also reflects increased exposures to other risk factors such as excessive alcohol use. This cohort study confirms the previously described findings of increased rates of liver fibrosis, with or without cirrhosis, in HIV/HCV co-infected patients compared to HCV mono-infected patients. This association remained highly significant even after careful adjustment for age and other factors associated with disease severity such as alcohol use, chronic hepatitis B infection, body-mass index and hepatitis C viral load. Within the subgroup of HIV/HCV co-infected individuals, the presence of clinically significant fibrosis was associated with lower CD4 cell counts and higher HIV viral loads, but interestingly not ART. These findings emphasize the importance of defining effective new treatment regimens for HCV in HIV co-infected individuals.*

3. 15 million accessing treatment

Routine inpatient provider-initiated HIV testing in Malawi, compared with client-initiated community-based testing, identifies younger children at higher risk of early mortality.

Preidis GA, McCollum ED, Kamiyango W, Garbino A, Hosseinipour MC, Kazembe PN, Schutze GE, Kline MW. J Acquir Immune Defic Syndr. 2013 May1;63(1):e16-22.

Objective: To determine **how routine inpatient provider-initiated HIV testing differs from traditional community-based client-initiated testing with respect to clinical characteristics of children identified and outcomes of outpatient HIV care.**

Design: Prospective observational cohort.

Methods: Routine clinical data were collected from children identified as HIV-infected by either testing modality in Lilongwe, Malawi, in 2008. After 1 year of outpatient HIV care at the Baylor College of Medicine Clinical Center of Excellence, outcomes were assessed.

Results: **Of 742 newly identified HIV-infected children enrolling into outpatient HIV care, 20.9% were identified by routine inpatient HIV testing. Compared with community-identified children, hospital-identified patients were younger (median 25.0 vs 53.5 months), with more severe disease (22.2% vs 7.8% WHO stage IV).** Of 466 children with known outcomes, 15.0% died within the first year of HIV care; median time to death was 15.0 weeks for community-identified children vs 6.0 weeks for hospital-identified children. The strongest predictors of early mortality were severe malnutrition (hazard ratio, 4.3; 95% confidence interval, 2.2-8.3), moderate malnutrition (hazard ratio, 3.2; confidence interval, 1.6-6.6), age < 12 months (hazard ratio, 3.2; 95% confidence interval, 1.4-7.2), age 12 to 24 months (hazard ratio, 2.5; 95% confidence interval, 1.1-5.7), and WHO stage IV (hazard ratio, 2.2; 95% confidence interval, 1.1-4.6). **After controlling for other variables, hospital identification did not independently predict mortality.**

Conclusions: **Routine inpatient HIV testing identifies a subset of younger HIV-infected children with more severe, rapidly progressing disease that traditional community-based testing modalities are currently missing.**

Abstract access

***Editor's notes**: Less than a quarter of children eligible for ART are receiving it, and one of the most important barriers is that HIV positive children are not diagnosed. Routine HIV counselling and testing of paediatric inpatients is a critical point of entry into HIV care. The longitudinal design of this study from Lilongwe, Malawi, compares long-term outcomes in children identified through provider-initiated testing and counselling (PITC) and community-based testing. The children identified through PITC were distinctly different from the community-identified children - being younger, more malnourished and with more advanced HIV disease and a higher early mortality rate. However, among those who survived to one year, the clinical profile was very similar to the children identified in the community. This study provides strong evidence for the role of PITC in identifying and treating young, high-risk, HIV positive children.*

High HIV testing uptake and linkage to care in a novel program of home-based HIV counseling and testing with facilitated referral in KwaZulu-Natal, South Africa.

van Rooyen H, Barnabas RV, Baeten JM, Phakathi Z, Joseph P, Krows M, Hong T, Murnane PM, Hughes J, Celum C J Acquir Immune Defic Syndr. 2013 May 24. [Epub ahead of print]

Objective: Home-based counseling and testing (HBCT) has demonstrated high HIV testing uptake in Africa. We piloted expanded HBCT-Plus, with point-of-care CD4 count testing and follow-up visits, as a strategy to increase linkage to HIV care and antiretroviral therapy (ART) uptake.

Methods: We conducted **universal, adult HBCT-Plus among contiguous households** in rural KwaZulu-Natal, South Africa; HIV-infected individuals received **point-of-care CD4 testing which was compared to CD4 results by flow cytometry**, **counseling and referral to care**. **Follow-up visits at months 1, 3 and 6 evaluated linkage to care and ART uptake.** Plasma viral load was measured at baseline and month 6.

Results: **671 adults were tested for HIV (91% coverage) and 201 (30%) were HIV-infected**. Median CD4 count was 435 cells/μL by point-of-care testing. There was **high agreement between the point-of-care and flow cytometry CD4 test results**; the mean difference was 16 cells/μL (CI: -1 to 32 cells/μL). **By month 3, 86% of those eligible (CD4 ≤200 cells/μL) had initiated ART**. Among 196 HIV-infected participants, mean viral load decreased by 0.31 log10 copies/mL (p=0.009) between baseline and month 6 and among those eligible for ART, mean PVL decreased by 2.46 log10 copies/mL (p=<0.001).

Conclusions: HBCT-Plus pilot achieved approximately 90% uptake of HIV testing, linkage to care and ART initiation, thus providing clinical and public health benefits, as demonstrated by a significantly decreased mean viral load. These data indicate a significant impact of HBCT-Plus on knowledge of HIV serostatus, linkage to HIV care, uptake of ART, adherence and reduced HIV infectiousness.

Abstract access

***Editor's notes**: This pilot study of integrated HBCT, with same day point-of-care CD4 testing, referral and follow-up provide encouraging data for future universal test and treat interventions. A high proportion of individuals linked into care upon the HBCT-plus intervention in this study - both amongst newly diagnosed individuals and those who previously knew their HIV positive status but had not accessed care. It is promising that the point-of-care CD4-count results and flow cytometry CD4-count results showed excellent agreement. Further, the authors describe the method as being feasible in a rural South African setting. The follow-up work on cost and cost-effectiveness will be highly pertinent to the potential wider roll out of this method. Finally, while the viral load reductions seen with this "cascade-enhancing" model may be modest overall given the ART initiation criteria in South Africa at the time of the study, they point to a beneficial effect. Further gains on viral load reduction would be reasonably expected with higher ART initiation thresholds.*

Mortality associated with delays between clinic entry and ART initiation in resource-limited settings: results of a transition-state model.

Hoffmann CJ, Lewis JJ, Dowdy DW, Fielding KL, Grant AD, Martinson NA, Churchyard GJ, Chaisson RE. J Acquir Immune Defic Syndr. 2013 May 1;63(1):105-111. doi: 10.1097/QAI.0b013e3182893fb4

To estimate the mortality impact of delay in antiretroviral therapy (ART) initiation from the time of entry into care. A state–transition Markov process model. This technique allows for assessing mortality before and after ART initiation associated with delays in ART initiation among a general population of ART-eligible patients without conducting a randomized trial. We used patient-level data from 3 South African cohorts to determine transition probabilities for pre-ART CD4 count changes and pre-ART and on-ART mortality. For each parameter, we generated probabilities and distributions for Monte Carlo simulations with 1-week cycles to estimate mortality 52 weeks from clinic entry. We estimated **an increase in mortality from 11.0% to 14.7% (relative increase of 34%) with a 10-week delay in ART** for patients entering care with our pre-ART cohort CD4 distribution. When we examined low CD4 ranges, the relative increase in mortality delays remained similar; however, the absolute increase in mortality rose. For example, **among patients entering with CD4 count 50–99 cells per cubic millimeter, 12-month mortality increased from 13.3% with no delay compared with 17.0% with a 10-week delay and 22.9% with a 6-month delay**. Delays in ART initiation, common in routine HIV programs, can lead to important increases in mortality. Prompt ART initiation for patients entering clinical care and eligible for ART, especially those with lower CD4 counts, could be a relatively low cost approach with a potential marked impact on mortality.

Abstract access

***Editor's notes**: Prompt initiation of ART in adults eligible for treatment is important to reduce mortality and morbidity, yet in some settings delays remain common. This is one of the first studies to attempt to estimate the impact of such delays on individual risk of mortality by modelling data collated from three well-characterized clinical cohorts in South Africa. A delay of 10 weeks might seem plausible in a routine programme setting and this led to an estimated 34% increased risk of 12-month mortality overall. The absolute impact of treatment delays was not surprisingly greatest for those with lowest CD4+ cell counts suggesting that particular effort should be focused on reducing treatment delays for these groups, perhaps by targeting groups for fast-track ART initiation (as is done in some settings). As health systems and resources in high burden settings continue to be stretched by high patient loads, it will be important to monitor and address delays in ART initiation.*

Ten-year mortality trends among persons diagnosed with HIV infection in England and Wales in the era of antiretroviral therapy: AIDS remains a silent killer.

Simmons RD, Ciancio BC, Kall MM, Rice BD, Delpech VC. HIV Med 2013 May 15 doi: 10.1111/hiv.12056 [Epub ahead of print]

We present **national trends in death rates and the proportion of deaths attributable to AIDS** in the era of effective antiretroviral therapy (ART), and **examine risk factors associated with an AIDS-related death**. Analyses of the national HIV-infected cohort for England and Wales linked to death records from the Office of National Statistics were performed. **Annual all-cause mortality rates were calculated by age group and sex for the years 1999–2008 and rates for 2008 were compared with death rates in the general population**. Risk factors associated with an AIDS-related death were investigated using a case–control study design. **The all-cause mortality rate among persons diagnosed with HIV infection aged 15–59 years fell over the decade: from 217 per 10 000 in 1999 to 82 per 10 000 in 2008**, with declines in all age groups and exposure categories except women aged 50–59 years and persons who inject drugs (rate fluctuations in both of these groups were probably a result of small numbers). **Compared with the general population (15 per 10 000 in 2008), death rates among persons diagnosed with HIV infection remained high,** especially in younger persons (aged 15–29 years) and persons who inject drugs (13 and 20 times higher, respectively). AIDS-related deaths accounted for 43% of all deaths over the decade (24% in 2008). **Late diagnosis (CD4 count < 350 cells/mL) was the most important predictor of dying of AIDS [odds ratio (OR) 10.55; 95% confidence interval (CI) 8.22–13.54]**. Sixty per cent of all-cause mortality and 81% of all AIDS-related deaths were attributable to late

diagnosis. Despite substantial declines, death rates among persons diagnosed with HIV infection continue to exceed those of the general population in the ART era. Earlier diagnosis could have prevented 1600 AIDS-related deaths over the decade. These findings highlight the need to intensify efforts to offer and recommend an HIV test in a wider range of clinical and community settings.

Abstract access

***Editor's notes**: In common with other data from high-income settings with widespread availability of ART, there has been a substantial decline in all-cause and HIV-related mortality in the decade between 1999 and 2008. However, at a population level mortality in persons diagnosed with HIV remains five-fold higher than in the general population (matched for age and sex). Late diagnosis was defined for this analysis as CD4+ cell count <350 cells/µl, although for some of the study period eligibility for ART in the UK would have been based on a threshold of <200 cells/µl. Using this definition, late diagnosis was the factor most strongly associated with mortality and around 3 in 5 deaths were attributable to late HIV diagnosis. It should be noted that these mortality estimates are based on individuals diagnosed with HIV infection and so don't account for persons with undiagnosed HIV, for whom mortality might be even higher. Overall, these data suggest that there is still much to be done to promote earlier access to HIV diagnosis in the UK and research should be focused on identifying effective HIV testing strategies in different community and health care settings.*

Improved retention associated with community-based accompaniment for antiretroviral therapy delivery in rural Rwanda.

Franke MF, Kaigamba F, Socci AR, Hakizamungu M, Patel A, Bagiruwigize E, Niyigena P, Walker KD, Epino H, Binagwaho A, Mukherjee J, Farmer PE, Rich ML. Clin Infect Dis. 2013 May;56(9):1319-26.

Background: Minimizing death and ensuring high retention and good adherence remain ongoing challenges for human immunodeficiency virus (HIV) treatment programs. We examined whether the **addition of community-based accompaniment** (characterized by daily home visits from a community health worker, directly observed treatment, nutritional support, transportation stipends, and other support as needed) **to the Rwanda national model for antiretroviral therapy (ART) delivery would improve retention in care, viral load suppression, and change in CD4 count, relative to the national model alone**.

Methods: We conducted a prospective observational cohort study among 610 HIV-infected adults initiating ART in 1 of 2 programs in rural Rwanda. Psychosocial and clinical characteristics were recorded at ART initiation. Death, treatment retention, and plasma viral load were assessed at 1 year. CD4 count was evaluated at 6-month intervals. Multivariable regression models were used to adjust for baseline differences between the 2 populations.

Results: **Eighty-five percent and 79% of participants in the community-based and clinic-based programs, respectively, were retained with viral load suppression at 1 year**. After adjusting for CD4 count, depression, physical health quality of life, and food insecurity, **community-based accompaniment was protective against death or loss to follow-up during the first year of ART** (hazard ratio, 0.17; 95% confidence interval [CI], .09-.35; P < .0001). In a second multivariable analysis, individuals receiving accompaniment were **more likely to be retained with a suppressed viral load at 1 year** (risk ratio: 1.15; 95% CI, 1.03-1.27; P = .01).

Conclusions: These findings indicate that **community-based accompaniment is effective in improving retention**, when added to a clinic-based program with fewer patient support mechanisms.

Abstract access

***Editor's notes**: One of the critical challenges facing ART programmes in resource-limited settings is ensuring that patients achieve high levels of adherence and remain engaged in care. This is important not only from an individual perspective, but also from a public health perspective by making best use of current investments, and minimizing the potential for emergence and transmission of resistance. Evaluations of interventions for improving adherence and retention have largely focused on single interventions (e.g. treatment supporters, mobile phone text reminders, or food supplements) and have had varying degrees of success. This may partly be because patients' adherence and retention in care is influenced by multiple factors acting at the level of the individual*

patient, healthcare system and community. In this prospective cohort study the authors demonstrate that a multi-faceted community intervention, which assists patients overcome structural barriers to accessing ART, can result in improved retention in care. Regardless of the intervention, >90% of patients in care at 12 months achieved viral suppression. This intervention was complex and labour intensive, involving daily visits by community healthcare workers (CHW) for monitoring of side effects and directly observed therapy, nutritional support, transport allowance and social support ranging from school fees to advice on micro-financing initiatives. The authors argue that the cost of such interventions, which may also have indirect benefits for the family, needs to be weighed up against the future cost of second-line ART and emerging resistance.

Long-Term Health Care Interruptions Among HIV-Positive Patients in Uganda.

Mills EJ, Funk A, Kanters S, Kawuma E, Cooper C, Mukasa B, Odit M, Karamagi Y, Mwehire D, Nachega J, Yaya S, Featherstone A, Ford N. J Acquir Immune Defic Syndr. 2013 May 1;63(1):e23-7

Background: Retaining patients in clinical care is necessary to ensure successful antiretroviral treatment (ART) outcomes. Among patients who discontinue care, some reenter care at a later stage, whereas others are or will be lost from follow-up. We examined **risk factors for health care interruptions and loss to follow-up** within a cohort receiving ART in Uganda.

Methods: Using a large hospital cohort providing free universal ART and HIV clinical care, we assessed characteristics and risk factors for **treatment interruptions, defined as a 12-month absence from care at Mildmay, and loss to follow-up, defined as absence from care greater than 12 months without reengagement in care at Mildmay**. We included patients aged 14 years and above. We assessed these outcomes over time using Kaplan-Meier analysis and multivariable regression.

Results: Of 6970 eligible patients, 784 (**11.2%) had a health care interruption** of at least 12 months and 217 (**3.1%) were lost to follow-up**. **Patients experiencing health care interruptions had higher baseline CD4 T-cell counts at ART initiation**, defined as ≥ 250 cells per cubic millimeter [odds ratio (OR): 1.29, 95% confidence intervals (CI): 1.11 to 1.50], **and lower levels of education** (OR: 1.32, 95% CI: 1.09 to 1.61). **Adolescents were much more likely to be lost to follow-up** (OR: 3.11, 95% CI: 2.23 to 4.34). In contrast, **having a partner** (OR: 0.22, 95% CI: 0.16 to 0.31) **or being sexually active at baseline** (OR: 0.40, 95% CI: 0.28 to 0.55) was **protective of loss to follow-up**.

Conclusions: Within this cohort, long periods of unsupervised health care interruptions were common.

Abstract access

***Editor's notes**: If the individual and public health benefits of antiretroviral therapy are to be realized then it is essential that patients remain engaged in care and adhere to antiretroviral therapy over the longer-term. Whilst some patients default from care and never return (loss to follow-up), others will return to care at a later time-point (unstructured treatment interruptions).Such treatment interruptions not only lead to increased morbidity and mortality, as demonstrated in the SMART study, but can also promote the development of drug resistance; however our understanding of the frequency, duration and determinants of unstructured treatment interruptions in resource-limited settings is limited.*

This article, from a well-established ART clinic in Uganda, helps improve our understanding of this issue. Despite very low levels of loss to follow-up, which the authors ascribed to the clinics' strong adherence support system, unstructured treatment interruptions of over 12 months duration were common (11.2%). Initiating ART at a higher CD4 count (>250 cells/mm^3), presumably whilst the patient was still relatively well, was a risk factor for treatment interruption. This finding may become even more pertinent in the future if the CD4 count threshold for initiating ART rises to 500 cells/mm^3. Whilst this study has focused on patient-level risk factors for unstructured treatment interruptions, future research must also explore contextual-level determinants, including those relating to the healthcare system itself. A greater understanding of these factors will help inform the successful development of interventions to support patients' long-term engagement in care.

Comparison of Tenofovir, Zidovudine, or Stavudine as Part of First-Line Antiretroviral Therapy in a Resource-Limited-Setting: A Cohort Study.

Velen K, Lewis JJ, Charalambous S, Grant AD, Churchyard GJ, Hoffmann CJ. PLoS One. 2013; 8(5): e64459

Background: **Tenofovir (TDF) is part of the WHO recommended first-line antiretroviral therapy (ART);** however, there are limited data comparing TDF to other nucleoside reverse transcriptase inhibitors in resource-limited-settings. Using a routine workplace and community-based ART cohort in South Africa, **we assessed single drug substitution, HIV RNA suppression, CD4 count increase, loss-from-care, and mortality between TDF, stavudine (d4T) 30 mg dose, and zidovudine (AZT).**

Methods**:** In **a prospective cohort study** we included ART naïve patients aged ≥17 years-old who initiated ART containing TDF, d4T, or AZT between 2007 and 2009. For analysis of single drug substitutions we used a competing-risks time-to-event analysis; for loss-from-care, mixed-effect Poisson modeling; for HIV RNA suppression, competing-risks logistic regression; for CD4 count slope, mixed-effects linear regression; and for mortality, proportional hazards modeling.

Results**: Of 6,196 patients, the initial drug was TDF for 665 (11%), d4T for 4,179 (68%), and AZT for 1,352 (22%). During the first 6 months of ART, the adjusted hazard ratio for a single drug substitution was 2.3 for d4T (95% confidence interval [CI]: 0.27, 19) and 5.2 for AZT (95% CI: 1.1, 23), compared to TDF; whereas, after 6 months, it was 10 (95% CI: 5.8, 18) and 4.4 (95% CI: 2.5, 7.8) for d4T and AZT, respectively**. Virologic suppression was similar by agent; however, CD4 count rise was lowest for AZT. **The adjusted hazard ratio for loss-from-care, when compared to TDF, was 1.5 (95% CI: 1.1, 1.9) for d4T and 1.2 (95% CI: 1.1, 1.4) for AZT. The adjusted hazard ratio for mortality, when compared to TDF, was 2.7 (95% CI: 2.0, 3.5) and 1.4 (95% CI: 1.3, 1.5) and for d4T and AZT, respectively.**

Discussion**:** In routine care**, TDF appeared to perform better than either d4T or AZT, most notably with less drug substitution and mortality than for either other agent.**

Abstract Full-text [free] access

Editor's notes*: South Africa has recently adopted TDF as first line therapy in place of D4T, in keeping with WHO recommendations. Despite the recent WHO guidance and the well documented side effect profiles of D4T and AZT, these NRTI's remain in widespread use in many resource-limited settings, mainly due to the higher cost of TDF. But as the authors of this paper highlight, it is not just the direct drug costs that need to be considered when deciding upon a first-line ART combination. When selecting an agent for long term use, the costs relating to monitoring, the management of toxicities, the frequency of regimen change, and the impact of loss to follow-up due to side effects all need to be considered. In this South African prospective cohort study, patients started on TDF had lower rates of drug substitution, both in the first 6 months of ART and after 6 months on ART, than patients started on AZT or D4T. Patients started on TDF also had a lower risk of mortality than those started on AZT or D4T, although rates of loss to follow-up were not consistently different according to initial choice of NRTI, and rates of virological suppression were similar with TDF, AZT and D4T. The study was limited by the fact that the vast majority of patients started on TDF were from workplace clinics (90%), whilst most of those starting D4T were from community clinics (98%) hence may not have been directly comparable; and the fact that the reasons for drug substitutions were not available to the investigators, meaning it is possible that a proportion of the substitutions from AZT or D4T during the study may not have been due to drug side effects. Overall however, these results provide preliminary evidence that TDF outperforms D4T and AZT in terms of the need for drug substitution and mortality outcomes, and support the WHO's recommendation for TDF as part of the first-line ART regimen.*

Association between efavirenz-based compared with nevirapine-based antiretroviral regimens and virological failure in HIV-infected children.

Lowenthal ED, Ellenberg JH, Machine E, Sagdeo A, Boiditswe S, Steenhoff AP, Rutstein R, Anabwani G, Gross R. JAMA. 2013 May 1;309(17):1803-9.

Worldwide, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine are commonly used in first-line antiretroviral regimens in both adults and children with human immunodeficiency virus (HIV) infection. Data on the comparative effectiveness of these medications in children are limited.

Objective**: To investigate whether virological failure is more likely among children who initiated 1 or the other NNRTI-based HIV treatment**.

Design, setting, and participants: Retrospective cohort study of children (aged 3-16 years) who initiated efavirenz-based (n = 421) or nevirapine-based (n = 383) treatment between April 2002 and January 2011 at a large pediatric HIV care setting in Botswana.

Main outcomes and measures: The primary outcome was time from initiation of therapy to virological failure. **Virological failure was defined as lack of plasma HIV RNA suppression to less than 400 copies/mL by 6 months or confirmed HIV RNA of 400 copies/mL or greater after suppression**. Cox proportional hazards regression analysis compared time to virological failure by regimen. Multivariable Cox regression controlled for age, sex, baseline immunologic category, baseline clinical category, baseline viral load, nutritional status, NRTIs used, receipt of single-dose nevirapine, and treatment for tuberculosis.

Results: With a **median follow-up time of 69 months** (range, 6-112 months; interquartile range, 23-87 months), **57/421 children (13.5%; 95% CI, 10.4%-17.2%) initiating treatment with efavirenz and 101/383 children (26.4%; 95% CI, 22.0%-31.1%) initiating treatment with nevirapine had virological failure.** There were 11 children (2.6%; 95% CI, 1.3%-4.6%) receiving efavirenz and 20 children (5.2%; 95% CI, 3.2%-7.9%) receiving nevirapine who never achieved virological suppression. The **Cox proportional hazard ratio for the combined virological failure end point was 2.0 (95% CI, 1.4-2.7; log rank P < .001, favoring efavirenz).** None of the measured covariates affected the estimated hazard ratio in the multivariable analyses.

Conclusions and relevance: Among children aged 3 to 16 years infected with HIV and treated at a clinic in Botswana, the **use of efavirenz compared with nevirapine as initial antiretroviral treatment was associated with less virological failure**. These findings may warrant additional research evaluating the use of efavirenz and nevirapine for pediatric patients.

Abstract access

Editor's notes*: Out of 3.4 million children infected with HIV world-wide, 90% live in sub-Saharan Africa. The majority of children initiating ART receive nevirapine-based regimens, a regimen in-line with WHO recommendations (children > 3 years old should receive nevirapine or efavirenz together with two drugs from the NRTI class). However, data regarding the relative effectiveness of nevirapine and efavirenz in children are limited. In this large retrospective clinic-based cohort study in Botswana rates of virological failure were found to be higher in patients initiating nevirapine as compared to those initiating efavIrenz (HR 2.0 [95% CI: 1.4-2.7; p<0.001). Whilst differences in effectiveness may be one explanation, the authors also discuss alternative explanations: drug interactions and resistance were thought to be unlikely as few patients were on anti-tuberculosis therapy, and only 2.2% of the cohort was known to have been exposed to single-dose nevirapine at birth. The role of sub-optimal adherence could not be assessed as, in common with many programme cohorts, data on adherence were limited. As highlighted by the authors, treatment decisions are rarely made randomly and are often influenced by the characteristics of the patients. Recognizing this limitation the authors explored whether female adolescents were more likely to be prescribed nevirapine (due to concerns about efavirenz in women of child-bearing age), with the underlying assumption that adolescents were more likely to exhibit sub-optimal adherence; however this did not explain the differences in virological outcomes. In summary, this study highlights the need for further research regarding the optimal first-line regimens in children.*

4. Avoid TB deaths

Identifying dynamic tuberculosis case-finding policies for HIV/TB co-epidemics.

Yaesoubi R, Cohen T. Proc Natl Acad Sci U S A. 2013 Jun 4;110(23):9457-62.

The global tuberculosis (TB) control plan has historically emphasized passive case finding (PCF) as the most practical approach for identifying TB suspects in high burden settings. The success of this approach in controlling TB depends on infectious individuals recognizing their symptoms and voluntarily seeking diagnosis rapidly enough to reduce onward transmission**. It now appears, at least in some settings, that more intensified case-finding (ICF) approaches may be needed to control TB transmission; these more aggressive approaches for detecting as-yet undiagnosed cases obviously require additional resources to implement.** Given that TB control programs are resource constrained and that the incremental yield of ICF is expected to wane over time as the pool of undiagnosed cases is depleted**, a tool that can help policymakers to identify when to implement or suspend an ICF intervention would be valuable.** In this article, we propose dynamic case-finding policies that **allow policymakers to use existing observations about the epidemic and resource availability to determine when to switch between PCF and ICF to efficiently use resources to optimize population health.** Using mathematical models of TB/HIV co-epidemics, we show that dynamic policies strictly dominate static policies that pre-specify a frequency and duration of rounds of ICF. We also find that the use of a diagnostic tool with better sensitivity for detecting smear-negative cases (e.g., Xpert MTB/RIF) further improves the incremental benefit of these dynamic case-finding policies.

Abstract access

***Editor's notes**: There is increasing recognition that to control the HIV-associated TB epidemic settings with high HIV prevalence, especially in southern Africa, that intensive TB case finding (ICF) rather than passive case finding (PCF) may be required. However, this is very resource-intensive and systematic reviews recently conducted by the WHO found weak evidence for an impact at an epidemiological level. Much more research is needed to define whether ICF is feasible, has a population level impact and is economically viable. The present modelling study suggests that dynamic case finding policies that switch between ICF and PCF based on simple inputs such as TB notification rate, budget etc. may provide a more cost-efficient means of case finding.*

5. Close the resource gap

Reproductive health priorities: evidence from a resource tracking analysis of official development assistance in 2009 and 2010.

Hsu J, Berman P, Mills A. Lancet. 2013 May 18;381(9879):1772-82.

Background: **Information is scarce about the extent to which official development assistance (ODA) is spent on reproductive health to provide childbirth care; support family planning; address sexual health; and prevent, treat, and care for sexually transmitted infections, including HIV**. We analysed flows of ODA to reproductive health for 2009 and 2010, assessed their distribution by donor type and purpose, and investigated the extent to which disbursements respond to need. We aimed to provide global estimates of aid to reproductive health, to assess the allocation of resources across reproductive health activities, and to encourage donor accountability in targeting aid flows to those most in need.

Methods: We applied a standard definition of reproductive health across all donors, including a portion of disease-specific activities and health systems development. **We analysed disbursements to reproductive health by donor type and purpose** (e.g., family planning). We also reported on an indicator to monitor donor disbursements: ODA to reproductive health per woman aged 15-49 years. **We analysed the extent to which funding is targeted to countries most in need**, proxied by female life expectancy at birth and prevalence of HIV infection in adults.

Findings: **Donor disbursements to reproductive health activities in all countries amounted to US$5579 million in 2009 and US$5637 million in 2010**-an increase of 1.0%. ODA for such activities in the 74 Countdown priority countries increased more rapidly at 5.3%. **More than half of the funding was directed towards prevention, treatment, and care of HIV infection for women of reproductive age** (15-49 years of age). On average, ODA to general reproductive health activities amounted to 15.9% and ODA to family planning 7.2%. Aid to reproductive health was heavily dependent on the USA, the Global Fund, the UK, the United Nations Population Fund, and the World Bank.

Interpretation: Donors are prioritising reproductive health, and the slight increase in funding in 2009-10 is welcome, especially in the present economic climate. **The large share of such funding for activities related to HIV infection** in women of reproductive age affects the amount of ODA received by priority countries. It **should thus be distinguished from resources directed to other reproductive health activities, such as family planning**, which has been the focus of recent worldwide advocacy efforts. Tracking of donor aid to reproductive health should continue to allow investigation of the allocation of resources across reproductive health activities, and to encourage donor accountability in targeting aid flows to those most in need..

Abstract access

***Editor's notes**: This study analyses the flows of official development assistance (ODA) to reproductive health in the context of the economic crisis. It is the first resource tracking to cover a more comprehensive set of female reproductive health activities, such as family planning and the treatment of sexually treated infections, including HIV. With a 1% increase in real terms, the study highlights the stability of ODA to reproductive health as promising, although the aggregate masks significant fluctuations by certain donors. Claiming more than half the total aid, funding for HIV activities dominates the package, while the 7.2% for family planning is of concern, given recent commitments. The study also finds that ODA disbursements are closely related to need and that this may even be improving slightly – this is encouraging in terms of the efficiency and effectiveness of aid to women's health priorities.*

Redefining global health-care delivery.

Kim JY, Farmer P, Porter ME. Lancet. 2013 May 17. pii: S0140-6736(13)61047-8.

Initiatives to address the unmet needs of those facing both poverty and serious illness have expanded significantly over the past decade. But many of them are designed in an ad-hoc manner to address one health problem among many; they are too rarely assessed; best practices spread slowly. When assessments of delivery do occur, they are often narrow studies of the cost-effectiveness of a single intervention rather than the complex set of them required to deliver value to patients and their families. **We propose a framework for** global health**-**care delivery **and evaluation** by considering efforts to introduce HIV/AIDS care to resource-poor settings. **The framework introduces the notion of** care delivery **value chains that apply a systems-level analysis to the complex processes and interventions that must occur, across a** health**-**care **system and over time, to deliver high-value** care **for patients with HIV/AIDS and co-occurring conditions**, from tuberculosis to malnutrition. To deliver value, vertical or stand-alone **projects must be integrated into shared** delivery **infrastructure so that personnel and facilities are used wisely and economies of scale reaped**. Two other integrative processes are necessary for delivering and assessing value in global health: one is the **alignment of** delivery **with local context by incorporating knowledge of both barriers to good outcomes** (from poor nutrition to a lack of water and sanitation) **and broader social and economic determinants of** health and wellbeing (jobs, housing, physical infrastructure). The second is the **use of effective investments in** care delivery **to promote equitable economic development**, especially for those struggling against poverty and high burdens of disease. We close by reporting our own shared experience of seeking to move towards a science of delivery by harnessing research and training to understand and improve care delivery.

Abstract access

***Editor's notes**: In this conceptual article, the authors propose a framework to guide effective health care delivery in resource-poor settings that builds on the concept of value chains from business management, in which production processes within firms are a chain of activities that produce valuable goods and services. In this framework, value is defined as a measure of aggregate health outcomes achieved per dollar spent, rather than health programme results. Rather than considering the intervention for a particular disease or condition as the basic unit of analysis, this framework suggests that value can be created at four levels, i.e. by integrating care for every individual medical condition, by using shared delivery infrastructure, by incorporating knowledge of local socio-economic constraints into care delivery, and finally by designing health systems to maximize their contribution to economic development. The authors provide another compelling rationale for the integration of health service delivery and systems, as well as complex external determinants of heath.*

6. Eliminate gender inequalities

The clinical implications of high rates of intimate partner violence against HIV-positive women.

Siemieniuk RA, Krentz HB, Miller P, Woodman K, Ko K, Gill MJ. J Acquir Immune Defic Syndr. 2013 May 24. [Epub ahead of print]

Introduction: Intimate partner violence (IPV) is associated with increased risk of HIV infection among women; however **whether IPV affects outcomes after HIV infection is uncertain**. We assess the impact of IPV on HIV-positive women.

Methods: All HIV-positive women who received outpatient HIV care in southern Alberta between March 2009 and January 2012 were screened for IPV. The associations with IPV of socio-demographic factors, health related quality of life, clinical status, and hospitalizations were obtained from a regional database and evaluated with multivariable regression analysis.

Results: Of 339 women screened, 137 (40.4%) reported experiencing IPV. **Those disclosing IPV had higher** rates of **smoking** [adjusted prevalence ratio (APR)=5.07; 95% confidence interval = 2.72-9.43; **illicit drug use** (APR=7.58, 2.45-23.26);a **history of incarceration** (APR=4.84, 1.85-12.68); **depression** (APR=2.50, 1.15-5.46); and **anxiety disorders** (APR=5.75, 2.10-15.63).Health related quality of life was diminished with IPV (APR=2.94, 1.40-6.16) for poor/fair vs. very good/excellent. **IPV-exposed women were hospitalized** 256 times /1000 patient-years compared to 166/1000 patient-years among IPV-unexposed (P<0.001). The relative risk was increased for **HIV-unrelated hospitalizations (1.42, 1.16-1.73**) and for **HIV-related hospitalizations after outpatient HIV care was initiated (2.19, 1.01-4.85**). **Modifiable contributors to the poor outcomes included decreased use of antiretroviral therapy** (APR=0.55, 0.34-0.91) and **additional interruptions in care longer than one year** (APR=1.90, 1.07-3.39).

Conclusions: **IPV is associated with deleterious HIV-related and HIV-unrelated health outcomes, of which suboptimal engagement in care is a contributor**. To improve outcomes, practitioners should aim to increase engagement in care of these women in particular.

Abstract access

***Editor's notes**: This is one of several papers published this month, looking at the issue of violence by an intimate partner (intimate partner violence) and HIV. Previous epidemiological research featured in HIV This Month has provided evidence that exposures to violence put women at increased HIV risk in Uganda. Importantly, this study looks at whether HIV positive women who have experienced violence have poorer clinical outcomes. The findings show the broad range of health issues that HIV positive IPV exposed women face – including depression and anxiety disorders. The analysis also shows that women who had been exposed to IPV had decreased and interrupted use of antiretroviral therapy, and increased hospitalization (both HIV unrelated and HIV related). These findings are not unique to women in Canada. One of the other papers published this month was among HIV positive women in an inner-city London clinic, and also found high levels of violence, including during pregnancy (Dhairyawan et al, 2013). Another was among gay and bisexual men in Canada which also found high levels of violence and an association with a history of childhood abuse and with poor clinical outcomes. In combination, the findings point to the urgent need to ensure that HIV clinical services are better equipped to address their client's exposures to intimate partner violence, both as an end in itself, as well as to help improve their HIV treatment prognosis.*

7. Eliminate stigma and discrimination

Living with HIV post diagnosis: a qualitative study of the experiences of Nairobi slum residents.

Wekesa E, Coast E. BMJ Open. 2013 May 3;3(5)

Objectives: To characterise **the experiences of heterosexual men and women living with HIV post diagnosis** and explain these experiences in relation to their identity and sexuality.

Design: Qualitative study using **in-depth interviews** and a theoretically informed biographic disruption theory.

Setting: Interviews were conducted in two Nairobi slums (Kenya).

Participants: 41 HIV-infected heterosexual men and women aged 18 years or older

Results: People living with HIV have **divergent experiences surrounding HIV diagnosis**. Post diagnosis, there are **multiple phases of identity transition, including status (non-) disclosure**, and **attempts at identity repair and normalcy**. For some people, this process involves **a transition to a new self-identity, incorporating both HIV and antiretroviral treatment (ART) into their lives**. For others, it involves a **partial transition, with some aspects of their pre diagnosis identity persisting, and for others it involves a rejection of HIV identity**. **Those people who were able to incorporate HIV/AIDS in their identity, without it being disruptive to their biography, were pursuing safer sexual and reproductive lives.** By contrast, those people with a more continuous biography continued to reflect their pre diagnosis identity and sexual behaviour.

Conclusions: **People living with HIV/AIDS (PLWHA) had to rework their sense of identity following diagnosis in the context of living in a slum setting**. Men and women living with HIV in slums are poorly supported by health systems and services as they attempt to cope with a diagnosis of HIV. Given the availability of ART, health services and professionals need to support the rights of PLWHA to be sexually active if they want to and achieve their fertility goals, while minimising HIV transmission risk.

Abstract Full-text [free] access

Editor's notes*: There is a need to understand the sexual health rights and needs of people living with HIV, especially in urban areas in sub-Saharan Africa where 72% of the population live in slums with poor access to services. In particular there are issues about stigma and disclosure post-diagnosis as well as concerns about risky sexually behaviour for those who are on ART. In the light of this the authors conducted qualitative research to understand the post-diagnosis experiences of slum dwellers in Nairobi. The authors used a theoretical concept of biographical disruption to understand how HIV acts as a disruptive experience on an individual's life, social relations, and identity. This theory entails three components: disruption of an individual's former behaviour and assumptions; changes in an individual's perception of self, and attempts to repair or change one's biography. To explore this, the authors conducted 41 in-depth interviews. For the paper they presented detailed analyses of three case studies to represent the wider sample of 41 participants. The findings revealed that reactions to HIV diagnosis represented a disruption of each individual's biography either experienced as shock, distress, or denial, or for one case study, relief. This reaction and their HIV status disclosure to others affected the incorporation of the new HIV positive identity. Assimilation and resources for identity normalization depended to a large extent on their access to social capital, through social support groups, community health workers or faith groups. It was also affected by taking up ART and pursuing a healthy role in society. However, the uptake of ARTs is dependent on people's hopes or uncertainties that the drugs will either make them well or more sick. Those that are able to assimilate HIV/AIDS in their identity without it being disruptive to their biography were pursuing safer sexual and reproductive lives. The authors suggest that because the process of incorporating an HIV positive identity is not predictable it is important that reaction to diagnosis, disclosure, social support, and uptake of ARTs for a healthy sexual life are discussed at diagnosis, and psychological support provided where an individual is unable to cope with their diagnosis.*

8. Strengthening HIV integration

Integration of Antiretroviral Therapy Services into Antenatal Care Increases Treatment Initiation during Pregnancy: A Cohort Study.

Stinson K, Jennings K, Myer L. PLoS One. 2013 May 16;8(5):e63328. Print 2013

Objectives: Initiation of antiretroviral therapy (ART) during pregnancy is critical to promote maternal health and prevent mother-to-child HIV transmission (PMTCT). The separation of services for antenatal care (ANC) and ART may hinder antenatal ART initiation. We **evaluated ART initiation during pregnancy under different service delivery models in Cape Town**, South Africa.

Methods: A **retrospective cohort study was conducted using routinely collected clinic data**. Three models for ART initiation in pregnancy were evaluated ART 'integrated' into ANC, ART located 'proximal' to ANC, and ART located some distance away from ANC ('distal'). Kaplan-Meier methods and Poisson regression were used to examine the association between service delivery model and antenatal ART initiation.

Results: Among 14 617 women seeking antenatal care in the three services, 30% were HIV-infected and 17% were eligible for ART based on CD4 cell count <200 cells/μL. **A higher proportion of women started ART antenatally in the integrated model compared to the proximal or distal models** (55% vs 38% vs 45%, respectively, global p=0.003). After adjusting for age and gestation at first ANC visit, **women who at the integrated service were significantly more likely to initiate ART antenatally** (rate ratio 1.33; 95% confidence interval: 1.09-1.64) compared to women attending the distal model; there was no difference between the proximal and distal models in antenatal ART initiation however (p=0.704).

Conclusions: **Integration of ART initiation into ANC is associated with higher levels of ART initiation in pregnancy.** This and other forms of service integration may represent a valuable intervention to enhance PMTCT and maternal health. .

Abstract Full-text [free] access

***Editor's notes**: This study highlights the challenges of successful delivery of effective PMTCT. The authors compare 3 PMTCT delivery sites with differing modes of care, principally with respect to distance between ANC and ART provision services. It must be noted that other baseline differences between study participants and site services also existed (such as algorithms of care and support from international agencies etc), however this is often seen in observational (and operational research) studies and the pertinence of the findings remain. An important result of this study is that even with integration of ANC and ART services, initiation of treatment was only achieved in just over half of eligible women. There was a notable trend in ART initiation by gestational age at presentation for ANC – the more advanced the gestational age at presentation, the less likely women were to start ART antenatally, reflecting delays in ART initiation even after a woman is in care. Many of the women proceeded to eventually start treatment postnatally. This is an important reminder of the missed opportunities that exist both for preventing HIV in infants and for earlier initiation of treatment in women for their own health.*

Effect of HIV infection on pregnancy-related mortality in sub-Saharan Africa: secondary analyses of pooled community-based data from the network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA).

Zaba B, Calvert C, Marston M, Isingo R, Nakiyingi-Miiro J, Lutalo T, Crampin A, Robertson L, Herbst K, Newell ML, Todd J, Byass P, Boerma T, Ronsmans C. Lancet. 2013 May 18;381(9879):1763-71.

Background: Model-based estimates of the global proportions of maternal deaths that are in HIV-infected women range from 7% to 21%, and the effects of HIV on the risk of maternal death is highly uncertain. We used longitudinal data from the Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA) network **to estimate the excess mortality associated with HIV during pregnancy and the post-partum period in sub-Saharan Africa**.

Methods: The **ALPHA network pooled data gathered between June, 1989 and April, 2012 in six community-based studies in eastern and southern Africa with HIV serological surveillance and verbal-autopsy reporting**. Deaths occurring during pregnancy and up to 42 days post partum were defined as pregnancy related. Pregnant or post-partum person-years were calculated for HIV-infected and HIV-uninfected women, and HIV-infected to HIV-uninfected mortality rate ratios and HIV-attributable rates were compared between pregnant or post-partum women and women who were not pregnant or post partum.

FINDINGS: **138,074 women aged 15-49 years contributed 636,213 person-years of observation. 49,568 women had 86,963 pregnancies. 6760 of these women died, 235 of them during pregnancy or the post-partum period.** Mean prevalence of HIV infection across all person-years in the pooled data was 17.2% (95% CI 17.0-17.3), but 60 of 118 (50.8%) of the women of known HIV status who died during pregnancy or post partum were HIV infected. **The mortality rate ratio of HIV-infected to HIV-uninfected women was 20.5 (18.9-22.4) in women who were not pregnant or post partum and 8.2 (5.7-11.8) in pregnant or post-partum women.**

Excess mortality attributable to HIV was 51.8 (47.8-53.8) per 1000 person-years in women who were not pregnant or post partum and 11.8 (8.4-15.3) per 1000 person-years in pregnant or post-partum women.

Interpretation: HIV-infected pregnant or post-partum women had around eight times higher mortality than did their HIV-uninfected counterparts. On the basis of this estimate, we predict that **roughly 24% of deaths in pregnant or post-partum women are attributable to HIV in sub-Saharan Africa**, suggesting that safe motherhood programmes should pay special attention to the needs of HIV-infected pregnant or post-partum women.

Abstract access

***Editor's notes**: This study is the first to estimate the contribution of HIV to mortality in pregnant and post-partum women using HIV sero-surveillance and verbal autopsy data from a network of studies in eastern and southern Africa. While there is variation by country, excess mortality due to HIV was considerably higher in non-pregnant women compared with pregnant/post-partum women. This is not entirely surprising as fertility falls with advancing HIV, so only healthier women with HIV conceive – the so-called 'healthy pregnant woman effect'. They are therefore less likely to die while pregnant/post-partum. However, the study estimates that almost a quarter of deaths in pregnant/post-partum women are attributable to HIV. This highlights the importance of integrating HIV into safe motherhood programmes. It is noteworthy that the majority of women at the time of this study would not have had access to antiretroviral treatment to benefit their own health (as opposed to single dose treatment to reduce mother-to-child transmission alone). While pointing to the potential benefits of the WHO PMTCT B option, the study emphasizes the potential further advantage of PMTCT B+ to reduce HIV related morbidity and mortality, both for women's own health and their unborn infants, with implications for current and future pregnancies.*

Evaluation of Using Routine Infant Immunization Visits to Identify and Follow-Up HIV-Exposed Infants and Their Mothers in Tanzania.

Goodson JL, Finkbeiner T, Davis NL, Lyimo D, Rwebembera A, Swartzendruber AL, Wallace AS, Kimambo S, Kimario CJ, Wiktor SZ, Luman ET. J Acquir Immune Defic Syndr. 2013 May 1;63(1):e9-e15

Background: **Without treatment, approximately half of HIV-infected infants die by age 2 years, and 80% die before age 5 years**. Early identification of HIV-infected and HIV-exposed infants provides opportunities for life-saving interventions. We **evaluated integration of HIV-related services with routine infant immunization** in Tanzania. METHODS: During April 2009 to March 2010, at 4 urban and 4 rural sites, mothers' HIV status was determined at first-month immunization using antenatal cards. HIV-exposed infants were offered HIV testing and follow-up care. Impact of integrated service delivery was assessed by comparing average monthly vaccine doses administered during the study period and a 2-year baseline period; acceptance was assessed by interviewing mothers and service providers. FINDINGS: **During 7569 visits, 308 HIV-exposed infants were identified and registered; of these, 290 (94%) were tested, 15 (5%) were HIV infected**. At urban sites, first-month vaccine doses remained stable (+2% for pentavalent vaccine and -4% for polio vaccine), and vaccine doses given later in life (pentavalent, polio, and measles) increased 12%, 8%, and 11%, respectively. **At rural sites, first-month vaccine doses decreased 33% and 35% and vaccine doses given later in life decreased 23%, 28%, and 28%. Mothers and service providers generally favored integrated services**; however, **HIV-related stigma and inadequate confidentiality controls of HIV testing were identified, particularly at rural sites**. INTERPRETATION: Integration of HIV-related services at immunization visits identified HIV-exposed infants, HIV-infected infants, and HIV-infected mothers; however, decreases in vaccine doses administered at rural sites were concerning. HIV-related service integration with immunization visits needs careful monitoring to ensure optimum vaccine delivery.

Abstract access

***Editor's notes**: One of the targets set in the Global Plan in 2009 was that there should be a 90% reduction in the number of children newly infected with HIV by 2015. Although progress has been made towards achieving this target, with a 24% reduction in HIV infections between 2009 and 2011, it is estimated that in 2011 alone 300 000 children in sub-Saharan Africa were newly infected with HIV. Despite the knowledge that antiretroviral therapy*

(ART) substantially reduces morbidity and mortality in children, only 23% of children eligible for treatment are estimated to be receiving ART; without access to ART these children will die. One of the major barriers to initiating ART, which urgently needs to be addressed, is access to HIV testing for children. This paper demonstrates the feasibility and acceptability of integrating routine HIV testing of mothers and infants into national immunization programmes. However, the implementation of such a strategy would have be to done with care, as the integration of HIV testing into immunization programmes may have a negative impact on vaccination uptake.

The Acceptability and Feasibility of Routine Pediatric HIV Testing in an Outpatient Clinic in Durban, South Africa.

Ramirez-Avila L, Noubary F, Pansegrouw D, Sithole S, Giddy J, Losina E, Walensky RP, Bassett IV Pediatr Infect Dis J. 2013

Background: Limited access to HIV testing for children impedes early diagnosis and access to ART. Our objective was to **evaluate the feasibility and acceptability of routine pediatric HIV testing** in an urban, fee-for-service, outpatient clinic in Durban, South Africa. METHODS: **We assessed the number of patients (0-15yrs) who underwent HIV testing upon physician referral during a baseline period**. **We then established a routine, voluntary HIV testing study for pediatric patients, regardless of symptoms.** Parents/caretakers were offered free rapid fingerstick HIV testing for their child. For patients <18mo, the biological mother was offered HIV testing and HIV DNA PCR was used to confirm the infant's status. The **primary outcome was the HIV testing yield, defined as the average number of positive tests per month during the routine compared to the baseline period**. RESULTS: Over a 5-month baseline testing period, 931pediatric patients registered for outpatient care. Of the 124 (13%) patients who underwent testing upon physician referral, 21 (17%, 95% CI 11-25%) were HIV-infected. During a **13-month routine testing period**, **2,790 patients registered for care and 2,106 (75%) were approached for participation**. Of these, **1,234 were eligible and 771(62%) enrolled**. Among those eligible, **637 (52%, 95% CI 49-54%) accepted testing for their child or themselves (biological mothers of infants <18 months)**.There was an **increase in the average number of HIV tests during the routine compared to the baseline HIV testing periods (49 vs. 25 tests per month, p=0.001) but no difference in the HIV testing yield during the testing periods (3 vs. 4 positive HIV tests/month, p=0.06).** However, during the routine testing period **HIV prevalence remains extraordinarily high with 39 (6%, 95% CI 4-8%)** newly-diagnosed HIV-infected children (median 7 years, 56% female). CONCLUSIONS: Targeted and symptom-based testing referral identifies an equivalent number of HIV-infected children as routine HIV testing. Routine HIV testing identifies a high burden of HIV and is a feasible and moderately acceptable strategy in an outpatient clinic in a high prevalence area.

Abstract access

***Editor's notes**: ART coverage of children in resource-limited settings is very low, in part because HIV positive children are being diagnosed late, or not at all. This has significant implications in terms of morbidity and mortality, as without access to treatment these children will die. Additionally late initiation of ART may result in irreversible conditions e.g. chronic lung disease. Routine HIV testing of children in an out-patient setting is one potential strategy which could be used to identify HIV positive children and link them into care. In this study the introduction of routine, voluntary HIV testing of children (0-15 years) into a general out-patient clinic in a high HIV prevalence setting, resulted in more children being tested than previously seen with provider-initiated testing. Despite this, no more HIV positive children were identified. One potential reason, as discussed in the paper, was selection bias; a significant proportion of children registering at the clinic did not have an HIV test. It is possible that children who were considered ineligible for testing, or whose caretakers either declined participation in the study or HIV testing, were at higher risk of being HIV positive. HIV positive children have the right to access life-saving ART; however as shown in this study routine voluntary testing was only moderately acceptable and as a result we may be failing to test those children who are at highest risk. Innovative solutions, such as opt-out testing need to be considered and debated at a national level.*