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HIV this month. Issue no. 8. August 2017

Welcome to the 8th issue of **HIV this month** in 2017! In this issue, we cover the following topics:

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UNAIDS

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1. HIV testing and treatment

HIV testing and the HIV epidemic –vitally important to prevent HIV becoming endemic

Editor's notes: *Epidemics refer to situations where the number of infections rises (and subsequently falls) more quickly than might be expected compared to a disease that is endemic. Endemic implies a stable situation, with natural fluctuations in the number of cases. Medley and Vassal have written a provocative article in Science that considers how differently individuals, communities and society react to epidemic rather than endemic diseases. They choose to call HIV in 2017 endemic, which carries a serious risk. As the authors state, "The contained public response, and the concurrent shift of responsibility to individuals to protect themselves from risk, means that endemic disease embeds itself further, as those at risk are often the very same people who do not have the private resources to avoid risk or access treatment." There are in fact multiple separate epidemics of HIV in different regions and in different populations. Some are rising and some are falling. The latest UNAIDS' report emphasizes the heterogeneity of HIV infections in the world. New HIV infections have fallen by 29% since 2010 in East and Southern Africa, the region with the highest rates. On the other hand, new HIV infections have risen by an alarming 60% in Eastern Europe and Central Asia over the same period, albeit from a much lower baseline. There is widespread political consensus to pursue the UN agenda endorsed at the High Level Meeting on Ending AIDS in New York last year. Let's not throw in the towel too soon!*

HIV testing services remain central to the HIV strategy and, as usual, this month there are several important papers on aspects of HIV testing, many of which illustrate challenges that need to be overcome.

There are several reasons to encourage people living with HIV to know their status. First and foremost, we know that the earlier treatment is started in the course of HIV, the better the outlook for the individual. People who start treatment become much less likely to transmit HIV infection to sexual partners. People who know their HIV status are also able to make informed decisions about their lives and their partnerships. A study this month by Escudero et al. from New York City used agent-based modelling to understand the testing and care continuum for people who inject drugs. Their results remind us of the key role of HIV testing. They estimated that 53% of the HIV transmission events from people who inject drugs arose from people who did not know their status, and a further 37% from people who had not been started ART. In other words, they estimate that only 10-11% of infections from people who inject drugs could be prevented by improving quality of care for people on treatment. The need to find effective ways to encourage people at risk to know their status and start treatment is stark.

Guanzhou is one of the largest cities in China, with a high population of migrants both national and international. It is among the most prosperous regions of Guangdong province and has the highest rates of HIV. Chen et al. added some HIV testing related questions to a wider population based health survey in two districts and showed that approximately a quarter of adults had previously been tested for HIV. HIV testing was almost all provided through free government facilities or blood transfusion centres. Despite early steps to make HIV self-testing more available, none of the 666 participants who answered the relevant questions in the survey had used a self-test. Distance from an HIV testing site was a key determinant of the likelihood of getting tested. It was not clear that people who might be at higher risk were more likely to be tested, although the numbers and sampling focused on the general population rather than people at special risk.

Wang et al. explored the different HIV test kits used in the first line screening in Xi'an. In line with Chinese guidelines, but not in line with WHO guidance on HIV testing algorithms for low prevalence

settings, they used third- or fourth-generation rapid tests and repeated the positive tests. WHO's algorithm for low prevalence settings includes three different rapid tests based on different antigens. Among 665 people found to be positive on rapid tests, only 559 were confirmed to be HIV-positive by Western blotting. Subsequent follow up with additional Western blots showed that two of the individuals in whom the first Western blot was indeterminate were seroconverting but the other 104 were HIV-negative and had had false-positive results on the original rapid tests. False positives were more likely with the fourth-generation test (22% of positive tests) compared to the various third-generation tests used (9-11% of positive tests). Fourth-generation assays are known to be more sensitive, detecting people with HIV around a week or two earlier in the window period than third-generation assays. However, the authors point out that in low prevalence settings like Xi'an, the known lack of specificity of fourth-generation assays means that they may not provide sufficient advantages to be used as the first line test. Overall, the paper emphasizes the importance of using clearly defined algorithms. The WHO algorithms no longer use Western blots, but do recommend using multiple tests based on different antigens for testing people at low risk of infection, and at least two different tests with different antigens for testing people at high risk of infection. Everyone should have additional confirmatory tests done prior to starting ART.

Harbertson et al. also focused on the accuracy of rapid diagnostic tests. They screened samples from 459 military personnel in seven African countries who had reported that they were HIV-positive. Using the WHO algorithm, they compared the results of quality assured HIV testing to the self-reported HIV status of the participants. They found that, in different country surveys, between three and 91% of people who said that they were living with HIV were in fact HIV-negative. The authors point out that several studies have demonstrated the importance of following the WHO guidance, and that the positive predictive value of a test (or algorithm) will always fall as the overall prevalence falls. They discuss possible limitations such as misunderstanding the question or the terminology used, but discount these possibilities as causing many of the false-positive reports, particularly given the highly variable results across different countries. There was a strong association between the likelihood of a false positive report and lower education level. People whose understanding of HIV was less good were also more likely to report themselves to be positive falsely. Overall, the authors assume that quality of testing services needs to be an important priority, while not discounting the challenges of using self-reports to collect information about HIV status.

As more and more people chose to know their HIV status, it may be possible to use routine data from the health service to track the epidemiology of HIV, rather than to use special surveys. Traditionally surveys of antenatal mothers have been used to monitor trends in the HIV epidemic over time. With the widespread adoption of routine testing for mothers, a large proportion of women have an HIV test. However, the assays used vary. For surveillance purposes, samples are often stored and transported as dried blood spots and assays are run in batches using automated ELISA technology. Routine testing (as discussed above) is often done using an algorithm based on a number of different rapid tests. Pereira et al. have explored the differences between these approaches among almost 40 000 Brazilian mothers who participated in the antenatal surveillance exercise. They interviewed mothers and linked their routine ANC results to the surveillance database. Overall the prevalence of HIV among expectant mothers in Brazil was similar whichever approach was used (0.36% or 0.38%). However, there were interesting differences. The performance accuracy in those found positive in the surveillance exercise (which was taken as the gold standard) was only 84% overall and varied between regions from 43% to 100%. So these 14 false negative results among the 88 individuals who were truly positive were compensated for in the overall prevalence estimates by a similar number (18) of false positive results among around 30 000 individuals who were truly negative. This highlights the challenges of providing accurate results to people in low prevalence settings. The 13% of mothers

who slipped through the routine services and were not tested or refused to be tested were significantly more likely to be HIV-positive (0.56%), reinforcing the potential biases involved. Finding 90% of people living with HIV will require considerable attention to the detail and the quality of HIV testing services.

Adolescents are often a population left behind, and regular reports show that adolescents living with HIV are less likely to know their status or to be on treatment or virally supressed. Simms et al. used provider initiated testing and counselling (PITC) in primary care clinics in Harare, Zimbabwe. For two years, the research team supported the routine offer of HIV testing to all six to 15 year olds presenting to seven clinics in a well-defined area of Harare. The authors then conducted a population-based survey to find out how many eight to 17 year olds (who had had two years of exposure to the intervention) were aware of their status. 141 (2.6%) were living with HIV and more than one-third of these were undiagnosed. Some had rarely been to the clinic, and others had been taken to the clinic by a guardian who was unable to consent to HIV testing on behalf of the child or the child's parents. Others had slipped through the PITC net, possibly because, as Lightfoot et al. in an accompanying comment suggest, providers still find it hard to offer HIV tests to everyone, as they assume that people living with HIV will not appear healthy. This fits with the researchers' findings that adolescents living with HIV who were currently healthy, had no skin or other problems and had parents who were alive were less likely to be diagnosed. Both papers suggest that community based testing is needed to find adolescents. However, this also raises challenges in settings with lower prevalence than the high-density suburbs of Harare chosen for this project. As prevalence falls lower than the 2.6% observed, a huge testing effort is needed, with attendant costs, but also (as explored above) with the risks of inaccurate results and of the very people that we want to find most, not being around for testing at the right moment.

When an emerging disease becomes endemic.

Medley GF, Vassall A. Science. 2017 Jul 14;357(6347):156-158. doi: 10.1126/science.aam8333.

Epidemics, such as HIV in the early 1980s and Ebola in 2014, **inspire decisive government investment and action, and individual and societal concern, sometimes bordering on panic**. By contrast, **endemic diseases**, such as HIV in 2017 and tuberculosis, **struggle to maintain the same attention**. For many, the paradox is that **endemic disease, in its totality, continues to impose a far higher public health burden than epidemic disease**. Overall, **the swift political response to epidemics has resulted in success**. It has proven possible to eradicate epidemic diseases, often without the availability of vaccines and other biomedical technologies. In recent times, **only HIV has made the transition from epidemic to endemic, but diseases that have existed for centuries continue to cause most of the infectious disease burden**.

Abstract access

The risk of HIV transmission at each step of the HIV care continuum among people who inject drugs: a modeling study.

Escudero DJ, Lurie MN, Mayer KH, King M, Galea S, Friedman SR, Marshall BL. BMC Public Health. 2017 Jul 25;17(1):614. doi: 10.1186/s12889-017-4528-9.

Background: People who inject drugs (PWID) are at continued risk for HIV in the U.S., and experience disparities across the HIV care continuum compared to other high-risk groups. Estimates of the risk of HIV transmission at each stage of the care continuum may assist in identifying public health priorities for averting incident infections among PWID, in addition to transmissions to sexual partners of PWID.

Methods: **We created an agent-based model simulating HIV transmission and the HIV care continuum for PWID in New York City (NYC) in 2012**. To account for sexual transmission arising from PWID to non-PWID, **the simulation included the entire adult NYC population**. **Using surveillance data and estimates from the National HIV Behavioral Surveillance system, we simulated a dynamic sexual and injecting network. We estimated the proportion of HIV transmission events attributable to PWID in the following categories**, those: **without an HIV diagnosis** ('Undiagnosed'); **diagnosed but not on antiretroviral therapy** (ART) ('Diagnosed - not on ART'); those **who initiated ART but were not virally suppressed** ('Unsuppressed'); and, those **who achieved viral suppression** ('Suppressed').

Results: **We estimated HIV incidence among PWID to be 113 per 100 000 person-years in 2012, with an overall incidence rate for the entire adult NYC population of 33 per 100 000 person-years**. Despite accounting for only 33% of the HIV-infected PWID population**, the Undiagnosed were associated with 52.6%** (95% simulation interval [95% SI]: 47.1-57.0%) **of total transmission events**. **The Diagnosed - not on ART population contributed the second-largest proportion of HIV transmissions, with 36.6%** (95% SI: 32.2-41.5%). **The Unsuppressed population contributed 8.7%** (95% SI: 5.6-11.8%), **and Suppressed 2.1%** (95% SI: 1.1-3.9%), relatively little of overall transmission.

Conclusion: **Among PWID in NYC, more than half (53%) of transmissions were from those who were unaware of their infection status and more than 36% were due to PWID who knew their status, but were not on treatment**. Our results indicate the importance of early diagnosis and interventions to engage diagnosed PWID on treatment to further suppress population-level HIV transmission. Future HIV prevention research should focus on the elimination of identified and potential barriers to the testing, diagnosis, and retention of PWID on HIV treatment.

Abstract Full-text [free] access

Is there a relationship between geographic distance and uptake of HIV testing services? A representative population-based study of Chinese adults in Guangzhou, China.

Chen W, Zhou F, Hall BJ, Tucker JD, Latkin C, Renzaho AMN, Ling L. PLoS One. 2017 Jul 20;12(7):e0180801. doi: 10.1371/journal.pone.0180801. eCollection 2017.

Achieving high coverage of HIV testing services is critical in many health systems, especially where HIV testing services remain centralized and inconvenient for many. As a result, planning the optimal spatial distribution of HIV testing sites is increasingly important. **We aimed to assess the relationship between geographic distance and uptake of HIV testing services among the general population in Guangzhou, China**. **Utilizing spatial epidemiological methods and stratified household random sampling, we studied 666 adults aged 18-59**. Computer-assisted interviews assessed self-reported HIV testing history. Spatial scan statistic assessed the clustering of participants who have ever been tested for HIV, and two-level logistic regression models assessed the association between uptake of HIV testing and the mean driving distance from the participant's residence to all HIV testing sites in the research sites. **The percentage of participants who have ever been tested for HIV was 25.2%** (168/666, 95%CI: 21.9%, 28.5%), **and the majority** (82.7%) of **participants tested for HIV in Centres for Disease Control and Prevention, public hospitals or STIs clinics. None reported using self-testing**. Spatial clustering analyses found a hotspot included 48 participants who have ever been tested for HIV and 25.8 expected cases (Rate Ratio = 1.86, P = 0.002). **Adjusted two-level logistic regression found an inverse relationship between geographic distance** (kilometers) **and ever being tested for HIV** (aOR = 0.90, 95%CI: 0.84, 0.96).

Married or cohabiting participants (aOR = 2.14, 95%CI: 1.09, 4.20) **and those with greater social support** (aOR = 1.04, 95%CI: 1.01, 1.07) **were more likely to be tested for HIV**. Our findings underscore the importance of considering the geographical distribution of HIV testing sites to increase testing. In addition, expanding HIV testing coverage by introducing non-facility based HIV testing services and self-testing might be useful to achieve the goal that 90% of people living with HIV knowing their HIV status by the year 2020.

Abstract Full-text [free] access

The characteristics of screening and confirmatory test results for HIV in Xi'an, China.

Wang L, Zhou KH, Zhao HP, Wang JH, Zheng HC, Yu Y, Chen W. PLoS One. 2017 Jul 7;12(7):e0180071. doi: 10.1371/journal.pone.0180071. eCollection 2017.

Objectives: Individuals with recent or acute HIV infection are more infectious than those with established infection**. Our objective was to analyze the characteristics of detection among HIV infections in Xi'an.**

Methods: **A 4th-generation kit** (Architect HIV Ag/Ab Combo) **and three 3rd-generationEIA kits** (WanTai, XinChuang and Livzon) **were used for HIV screening. Overall, 665 individuals were identified as positive and were tested by western blotting** (WB). **The characteristics of the screening and confirmatory tests were analyzed, including the band patterns, the early detection performance and the false-positive rates.**

Results: **In total, 561 of the 665 patients were confirmed as having HIV-1 infection, and no HIV-2 specific band was observed**. **Among these 561 WB-positive cases, reactivity to greater than or equal to 9 antigens was the most commonly observed pattern (83.18%), and the absence of reactivity to p17, p31 and gp41 was detected in 6.44%, 5.9% and 2.86% of the cases, respectively**. Two cases were positive by the 4th-generation assay but negative by the 3rd-generation assay for HIV screening and had seroconversion. **The false-positive rate of the Architect HIV Ag/Ab Combo (22.01%) was significantly higher than those of WanTai (9.88%), XinChuang (10.87%) and Livzon (8.93%), $p<0.05$**

Conclusion: **HIV infection in Xi'an is mainly caused by HIV-1, and individuals are rarely identified at the early phase.** Although the false-positive rate of the 4th-generation assay was higher than that of the 3rd-generation assay, it is still recommended for use as the initial HIV screening test for high-risk individuals. In Xi'an, a 3rd-generation assay for screening could be considered.

Abstract Full-text [free] access

Self-reported HIV-positive status but subsequent HIV-negative test result using rapid diagnostic testing algorithms among seven sub-Saharan African military populations.

Harbertson J, Hale BR, Tran BR, Thomas AG, Grillo M, Jacobs MB, McAnany J, Shaffer RA. PLoS One. 2017 Jul 7;12(7):e0180796. doi: 10.1371/journal.pone.0180796. eCollection 2017.

HIV rapid diagnostic tests (RDTs) combined in an algorithm are the current standard for HIV diagnosis in many sub-Saharan African countries, and extensive laboratory testing has confirmed HIV RDTs have excellent sensitivity and specificity. However, false-positive RDT algorithm results have been reported due to a variety of factors, such as suboptimal quality assurance procedures and inaccurate interpretation of results. **We conducted HIV serosurveys in seven sub-Saharan African military populations and recorded the frequency of personnel self-reporting HIV positivity, but**

subsequently testing HIV-negative during the serosurvey. **The frequency of individuals who reported they were HIV-positive but subsequently tested HIV-negative using RDT algorithms ranged from 3.3 to 91.1%, suggesting significant rates of prior false-positive HIV RDT algorithm results, which should be confirmed using biological testing across time in future studies**. Simple measures could substantially reduce false-positive results, such as greater adherence to quality assurance guidelines and prevalence-specific HIV testing algorithms as described in the World Health Organization's HIV testing guidelines. Other measures to improve RDT algorithm specificity include classifying individuals with weakly positive test lines as HIV indeterminate and retesting. While expansion of HIV testing in resource-limited countries is critical to identifying HIV-infected individuals for appropriate care and treatment, careful attention to potential causes of false HIV-positive results are needed to prevent the significant medical, psychological, and fiscal costs resulting from individuals receiving a false-positive HIV diagnosis.

Abstract Full-text [free] access

Transitioning from antenatal surveillance surveys to routine HIV testing: a turning point in the mother-to-child transmission prevention programme for HIV surveillance in Brazil.

Pereira GFM, Sabidó M, Caruso A, Benzaken AS. BMC Infect Dis. 2017 Jul 5;17(1):469. doi: 10.1186/s12879-017-2540-4.

Background: In Brazil, due to the rapid increase in programmes for the prevention of mother-to-child transmission (PMTCT), routine programme data are widely available**. The objective of this study was to assess the utility of programmatic data to replace HIV surveillance based on the antenatal care (ANC) surveillance survey (SS).**

Methods**: We analysed ANC SS data from 219 maternity service clinics. PMTCT variables were extracted from the ANC SS data collection form, which allowed us to capture and compare the ANC SS data and PMTCT HIV test results for each pregnant woman who completed the ANC SS**. Both the PMTCT programme and the ANC SS tested for HIV using sequential ELISA and western blot for confirmation. We assessed the completeness (% missing) of the PMTC data included in the ANC SS.

Results: **Of the 36 713 pregnant women who had ANC SS HIV tests performed, 30 588 also underwent PMTCT HIV testing. The HIV prevalence rate from routine PMTCT testing was 0.36%, compared to 0.38% from the ANC SS testing** (relative difference -0.05%; absolute difference -0.02%). **The relative difference in prevalence rates between pregnant women in northern Brazil and pregnant women central-west Brazil was -0.98 and 0.66, respectively**. Of the 29 856 women who had HIV test results from both the PMTCT and ANC SS, **the positive percent agreement of the PMTCT versus the surveillance test was 84.1%** (95% confidence interval [CI]: 74.8-91.0), **and the negative percent agreement was 99.9%** (95% CI: 99.9-100.0). The PMTCT HIV testing uptake was 86.4%. The ANC SS HIV prevalence was 0.33% among PMTCT non-refusers and 0.59% among refusers, with a percent bias of -10.80% and a differential prevalence ratio of 0.56. Syphilis and HIV testing results were complete in 98% and 97.6% of PMTCT reports, respectively. The reported HIV status for the women at clinic entry was missing.

Conclusion: **Although there were consistent HIV prevalence estimates from the PMTCT data and the ANC SS, the overall positive percent agreement of 84.1% falls below the World Health Organization benchmark of 94.7%.** Therefore, Brazil must continue to reinforce data collection practices and ensure the quality of recently introduced rapid HIV testing before replacing the PMTCT

data with surveillance techniques. However, some regions with better results could be prioritized to pilot the use of PMTCT data for surveillance.

Abstract Full-text [free] access

Community burden of undiagnosed HIV infection among adolescents in Zimbabwe following primary healthcare-based provider-initiated HIV testing and counselling: A cross-sectional survey.

Simms V, Dauya E, Dakshina S, Bandason T, McHugh G, Munyati S, Chonzi P, Kranzer K, Ncube G, Masimirembwa C, Thelingwani R, Apollo T, Hayes R, Weiss HA, Ferrand RA. PLoS Med. 2017 Jul 25;14(7):e1002360. doi: 10.1371/journal.pmed.1002360. eCollection 2017 Jul.

Background: Children living with HIV who are not diagnosed in infancy often remain undiagnosed until they present with advanced disease. Provider-initiated testing and counselling (PITC) in health facilities is recommended for high-HIV-prevalence settings, but it is unclear whether this approach is sufficient to achieve universal coverage of HIV testing. **We aimed to investigate the change in community burden of undiagnosed HIV infection among older children and adolescents following implementation of PITC in Harare, Zimbabwe.**

Methods and Findings: **Over the course of 2 years (January 2013-January 2015), 7 primary health clinics (PHCs) in southwestern Harare implemented optimised, opt-out PITC for all attendees aged 6-15 years**. **In February 2015-December 2015, we conducted a representative cross-sectional survey of 8-17-year-olds living in the 7 communities served by the study PHCs, who would have had 2 years of exposure to PITC**. Knowledge of HIV status was ascertained through a caregiver questionnaire, and anonymised HIV testing was carried out using oral mucosal transudate (OMT) tests. After 1 participant taking antiretroviral therapy was observed to have a false negative OMT result, from July 2015 urine samples were obtained from all participants providing OMTs and tested for antiretroviral drugs to confirm HIV status. Children who tested positive through PITC were identified from among survey participants using gender, birthdate, and location. **Of 7146 children in 4251 eligible households, 5486 (76.8%) children in 3397 households agreed to participate in the survey, and 141 were HIV positive. HIV prevalence was 2.6% (95% CI 2.2%-3.1%), and over a third of participants with HIV were undiagnosed (37.7%; 95% CI 29.8%-46.2%). Similarly, among the subsample of 2643 (48.2%) participants with a urine test result, 34.7% of those living with HIV were undiagnosed (95% CI 23.5%-47.9%).** Based on extrapolation from the survey sample to the community, we estimated that PITC over 2 years identified between 18% and 42% of previously undiagnosed children in the community. **The main limitation is that prevalence of undiagnosed HIV was defined using a combination of 3 measures (OMT, self-report, and urine test), none of which were perfect.**

Conclusions: **Facility-based approaches are inadequate in achieving universal coverage of HIV testing among older children and adolescents**. Alternative, community-based approaches are required to meet the Joint United Nations Programme on HIV/AIDS (UNAIDS) target of diagnosing 90% of those living with HIV by 2020 in this age group.

Abstract Full-text [free] access

Old fashioned AIDS is still with us – shocking in 2017

Editor's notes: *The term AIDS refers to advanced HIV disease with a CD4 count below 200 cells per microl. or with one of several typical opportunistic infections. It is more than twenty years since the revolutionary discovery of highly active combination antiretroviral therapy. While deaths due to HIV*

have fallen steadily over the past two decades, it is shocking that so many people are still dying from AIDS. In part this is due to the same issues of HIV testing discussed above. The Centers for Disease Control and Prevention (CDC) published their most recent report on surveillance in the United States of America (USA). The authors show very gradual progress in the right direction. But, still more than 20% of people are diagnosed with HIV infection in the USA when they already have AIDS. In fact, in a further 20% of people, the stage of infection was not reported to CDC, so as a proportion of those with a known stage at diagnosis, as many as one quarter were diagnosed with AIDS. As might be expected, there are disparities between states with District of Columbia and California doing a little better. There are big disparities by age (with over one third of people diagnosed at age greater than 45 years having AIDS) but surprisingly little difference by ethnicity.

Médecins sans Frontières (MSF) recently released a report highlighting the challenge of advanced disease, which was picked up in a commentary in the British Medical Journal by Cousins. The report points out that in hospital settings in Democratic Republic of Congo, Guinea, Kenya, and Malawi, MSF are still seeing an alarmingly high mortality rate, with one third of deaths occurring within the first 48 hours of admission. As many as three quarters of the patients had been on antiretroviral therapy (ART), suggesting that their advanced disease was not a consequence of late presentation, but rather of failure of the health system to deliver quality care. The importance of detecting treatment failure early and changing to effective second (or third) line ART was emphasized. Once patients do present to hospital with advanced HIV disease, it is a clinical emergency and urgent effective care may make a big difference. WHO has recently issued guidance on managing advanced HIV disease, and the Journal of the International AIDS Society has recently released a useful supplement on Differentiated Care and HIV.

Back in the USA, Braunstein et al. used existing laboratory and other data to construct a retrospective analysis of what happened in the intervenable period during which different treatment approaches might have prevented more than 11 000 people from dying with HIV between 2007 and 2013. The intervenable period was defined as the 12 months before the last three months of life. The authors pointed out that in the last three months of life, people might be in care that was not typical of their engagement during the preceding year. So the intervenable period is therefore more important to see where change could happen. Like the MSF team, they found that a substantial proportion of people were not properly treated, as shown by the finding that 60% of people did not have a suppressed viral load in the period analysed. This was despite 98% having some engagement with the health system as shown by laboratory records, 80% being defined as linked to care, and 76% being prescribed ART. The challenge seemed to be to provide high quality care with continuity of care and decisions made promptly according to the findings in the laboratory.

The package of interventions recommended by WHO in their guidance for people presenting with advanced HIV disease includes screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions. Additional support for this approach comes from the REALITY randomized trial conducted by Hakim and colleagues in Uganda, Zimbabwe, Malawi, and Kenya. In this trial, people with advanced HIV infection, judged by their CD4 count, were randomized in a factorial design. 1805 participants were randomized to different ART regimens; to nutritional support or not; and to a package of prophylaxis. This paper reports on the differences seen according to whether or not participants were randomized to receive the enhanced prophylaxis. The package consisted of at least 12 weeks of co-trimoxazole (against pneumocystis, malaria, and various bacterial and protozoal infections), co-formulated with isoniazid and pyridoxine (against tuberculosis), along with fluconazole (against cryptococcus, candida and other fungi) also for 12 weeks and azithromycin (against a broader range of invasive bacteria including salmonella) for five days. The enhanced prophylaxis led to a 27% reduction in mortality six

months after entering the study, and there was still a clear difference after one year, by when 127 people had died in the standard of care group compared to 98 in the enhanced prophylaxis group. Nonetheless, the death rate was still considerable. It is also worth noting that many of the people in whom the CD4 count was extremely low did not complain of any symptoms. So CD4 testing is still needed at the point of clinical care to determine who needs urgent differentiated care for advanced HIV infection.

The final paper in this section is a randomised trial from GHESKIO in Haiti (Koenig et al.). The investigators randomized 701 people diagnosed with HIV, to start ART on the same day as their diagnosis, or to wait for three weeks, as is standard of care at the centre. 12 months later, viral suppression was somewhat better in people who started ART on the same day (61% vs. 52% at a cut-off of 1000 copies per ml.). The authors point out that this was a single centre study, and results from GHESKIO might not be generalizable to other treatment sites in Haiti. Although there were still substantial losses to follow up, there was clearly no evidence that the policy to start people on HIV treatment immediately was too hasty.

Missed opportunities: adapting the HIV care continuum to reduce HIV-related deaths

Braunstein SL, Robbins RS, Daskalakis DC. J Acquir Immune Defic Syndr. 2017 Jul 26. doi: 10.1097/QAI.0000000000001509. [Epub ahead of print]

Introduction: With advances in HIV care, persons with HIV/AIDS (PWHA) can lead healthy lives, but avoidable, HIV-related deaths continue to occur in New York City (NYC).

Methods: **We selected PWHA from our surveillance registry who died between 2007-2013, resided in NYC, and survived ≥15 months post-diagnosis to generate an HIV Mortality Reduction Continuum of Care (HMRCC) describing pre-death care patterns among PWHA**. **We used HIV laboratory test reports to measure care outcomes during an "intervenable period" (IP) during which deaths may have been avoided.** The continuum was stratified by underlying cause of death (COD) (HIV-related vs. other), and the HIV-related HMRCC was stratified by demographic characteristics.

Results: **11 187 analysis-eligible PWHA died during 2007-2013. 98% linked to care; 80% were retained in care during the IP; 66% were prescribed ART; 47% had VL≤1500 copies/mL; 40% achieved viral suppression (VS). Half (47%) of deaths were HIV-related. Retention was higher among HIV-related COD (83% vs. 78%), but VS was lower (34% vs. 46%). The HIV-related HMRCC revealed disparities in VS**. Despite comparable retention rates, Whites had the highest VS (42%, vs. 32% Blacks and 33% Latinos/Hispanics). Additionally, retention and VS increased with increasing age. People with a history of injection drug use had relatively high rates of retention (88%) and VS (37%).

Discussion: The HMRCC is a novel framework for evaluating pre-death care patterns among PWHA and identifying opportunities to reduce preventable deaths. **In NYC, reducing mortality will require increasing VS among those already in care, particularly for Blacks and Latinos/Hispanics**.

Abstract access

Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa

Hakim J, Musiime V, Szubert AJ, Mallewa J, Siika A, Agutu C, Walker S, Pett SL, Bwakura-Dangarembizi M, Lugemwa A, Kaunda S, Karoney M, Musoro G, Kabahenda S, Nathoo K, Maitland

K, Griffiths A, Thomason MJ, Kityo C, Mugyenyi P, Prendergast AJ, Walker AS, Gibb DM; REALITY Trial Team. N Engl J Med. 2017 Jul 20;377(3):233-245. doi: 10.1056/NEJMoa1615822.

Background: In sub-Saharan Africa, among patients with advanced human immunodeficiency virus (HIV) infection, the rate of death from infection (including tuberculosis and cryptococcus) shortly after the initiation of antiretroviral therapy (ART) is approximately 10%.

Methods: **In this factorial open-label trial conducted in Uganda, Zimbabwe, Malawi, and Kenya, we enrolled HIV-infected adults and children 5 years of age or older who had not received previous ART and were starting ART with a CD4+ count of fewer than 100 cells per cubic millimeter**. They underwent simultaneous randomization to receive enhanced antimicrobial prophylaxis or standard prophylaxis, adjunctive raltegravir or no raltegravir, and supplementary food or no supplementary food. **Here, we report on the effects of enhanced antimicrobial prophylaxis, which consisted of continuous trimethoprim-sulfamethoxazole plus at least 12 weeks of isoniazid-pyridoxine** (co-formulated with trimethoprim-sulfamethoxazole in a single fixed-dose combination tablet)**, 12 weeks of fluconazole, 5 days of azithromycin, and a single dose of albendazole, as compared with standard prophylaxis** (trimethoprim-sulfamethoxazole alone). **The primary end point was 24-week mortality.**

Results: **A total of 1805 patients** (1733 adults and 72 children or adolescents) **underwent randomization to receive either enhanced prophylaxis** (906 patients) **or standard prophylaxis** (899 patients**) and were followed for 48 weeks** (loss to follow-up, 3.1%). **The median baseline CD4+ count was 37 cells per cubic millimeter, but 854 patients (47.3%) were asymptomatic or mildly symptomatic.** In the Kaplan-Meier analysis at 24 weeks, the rate of death with enhanced prophylaxis was lower than that with standard prophylaxis (80 patients [8.9% vs. 108 [12.2%]; hazard ratio, 0.73; 95% confidence interval [CI], 0.55 to 0.98; P=0.03); 98 patients (11.0%) and 127 (14.4%), respectively, had died by 48 weeks (hazard ratio, 0.76; 95% CI, 0.58 to 0.99; P=0.04). **Patients in the enhanced-prophylaxis group had significantly lower rates of tuberculosis** (P=0.02), **cryptococcal infection** (P=0.01), **oral or esophageal candidiasis** (P=0.02), **death of unknown cause** (P=0.03), **and new hospitalization** (P=0.03). However, there was no significant between-group difference in the rate of severe bacterial infection (P=0.32). There were nonsignificantly lower rates of serious adverse events and grade 4 adverse events in the enhanced-prophylaxis group (P=0.08 and P=0.09, respectively**). Rates of HIV viral suppression and adherence to ART were similar in the two groups.**

Conclusion: **Among HIV-infected patients with advanced immunosuppression, enhanced antimicrobial prophylaxis combined with ART resulted in reduced rates of death at both 24 weeks and 48 weeks without compromising viral suppression or increasing toxic effects.**

Abstract Full-text [free] access

Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial

Koenig SP, Dorvil N, Dévieux JG, Hedt-Gauthier BL, Riviere C, Faustin M, Lavoile K, Perodin C, Apollon A, Duverger L, McNairy ML, Hennessey KA, Souroutzidis A, Cremieux PY, Severe P, Pape JW. PLoS Med. 2017 Jul 25;14(7):e1002357. doi: 10.1371/journal.pmed.1002357. eCollection 2017 Jul.

Background: Attrition during the period from HIV testing to antiretroviral therapy (ART) initiation is high worldwide. **We assessed whether same-day HIV testing and ART initiation improves retention and virologic suppression**.

Methods and Findings: **We conducted an unblinded, randomized trial of standard ART initiation versus same-day HIV testing and ART initiation among eligible adults ≥18 years old with World Health Organization Stage 1 or 2 disease and CD4 count ≤500 cells/mm^3**. The study was conducted **among outpatients at the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic infections** (GHESKIO) **Clinic in Port-au-Prince, Haiti**. **Participants were randomly assigned (1:1) to standard ART initiation or same-day HIV testing and ART initiation**. The standard group initiated ART 3 weeks after HIV testing, and the same-day group initiated ART on the day of testing. **The primary study endpoint was retention in care 12 months after HIV testing with HIV-1 RNA <50 copies/ml.** We assessed the impact of treatment arm with a modified intention-to-treat analysis, using multivariable logistic regression controlling for potential confounders. **Between August 2013 and October 2015, 762 participants were enrolled; 59 participants transferred to other clinics during the study period, and were excluded as per protocol, leaving 356 in the standard and 347 in the same-day ART groups**. In the standard ART group, 156 (44%) participants were retained in care with 12-month HIV-1 RNA <50 copies, and 184 (52%) had <1000 copies/ml; 20 participants (6%) died. In the same-day ART group, 184 (53%) participants were retained with HIV-1 RNA <50 copies/ml, and 212 (61%) had <1000 copies/ml; 10 (3%) participants died. The unadjusted risk ratio (RR) of being retained at 12 months with HIV-1 RNA <50 copies/ml was 1.21 (95% CI: 1.04, 1.38; p = 0.015) for the same-day ART group compared to the standard ART group, and the unadjusted RR for being retained with HIV-1 RNA <1000 copies was 1.18 (95% CI: 1.04, 1.31; p = 0.012). **The main limitation of this study is that it was conducted at a single urban clinic, and the generalizability to other settings is uncertain**.

Conclusions: **Same-day HIV testing and ART initiation is feasible and beneficial in this setting, as it improves retention in care with virologic suppression among patients with early clinical HIV disease**.

Abstract Full-text [free] access

2. Elimination of childhood infections

Women know what they want, but need more reproductive health choices

Editor's notes: *Eliminating new HIV infections among children is often seen as a useful barometer of the overall success of the health systems as it relates to HIV. Combination prevention approaches that include structural, behavioural and biomedical elements reduce the chance of women becoming HIV-positive. Effective provision of a range of choices of modern contraceptive technology allow women to choose whether and when to have babies. The option B+ approach should ensure that all pregnant women living with HIV are offered lifelong ART, which minimises the chance of mother to child transmission of HIV infection. Continuing ART treatment for life keeps the mother healthy and allows her to support the development of her infant.*

New HIV infections in children have declined by 46% since 2010, but there were still an estimated 160 000 new infections in 2016. We know that in many settings the health system barometer is still forecasting plenty of clouds among the bright spells. This month saw a range of papers describing reproductive health choices and HIV, as well as reflections on how option B+ is working, now that it is standard of care.

Contraceptive choices for women at high risk of HIV or living with HIV are complicated. WHO recently reclassified long-acting progestin injections, such as DMPA, for women at high risk of HIV infection as category 2 in the Medical Eligibility for Contraception guidance. Category 2 means that, although the

method is generally safe to use, clinical judgment and careful follow up may be required. While the evidence comes from meta-analyses of observational studies, with inherent limitations, there is a reliable association between new HIV infection and the use of injectable progestins. The ongoing randomized ECHO trial will provide higher quality evidence of causality, but results will not be reported until 2019.

Mayhew et al. found that women living with HIV attending clinics in Kenya, were quite clear about their fertility intentions. Many did not want more children, although they acknowledged pressure from partners and others. Stigma around breast-feeding, worries about money and about possible health consequences of pregnancy were all reasons to decide not to have further children. The large majority used various sorts of contraception, but despite this 40% of pregnancies during the study were unintended. The authors felt that the advice given by the clinics was not adequate and that choice of contraceptive method was limited. In particular reliable long-acting methods, both reversible and not, were rarely taken up by the younger women. Overall 16% of women used long-acting methods, and no pregnancies occurred in this group.

Chanda et al. focused on female sex workers in Zambia and found similar results. Almost half the women had had terminations of pregnancies, and 62% of pregnancies were not planned. Interestingly the availability of condoms at their places of work reduced the chances of unwanted pregnancy. Approximately 39% used injectable long-acting contraceptives and only 18% used dual protection with a barrier in addition to a non-barrier method. Less than one-third of the women reported that condoms were available often or always at work, and 23% reported using no contraception. Providing access to condoms for sex workers in the highest transmission areas of countries like Zambia seems such an obvious pre-requisite for HIV programmes that it is extraordinary that in 2017 we still do not manage to do so.

Finally on this theme, Salters et al. demonstrate that contraceptive choice for women living with HIV is not only a challenge in sub-Saharan Africa. The authors followed women in the Canadian HIV Women's Sexual and Reproductive Health Cohort Study and showed that 61% of reported pregnancies were unintended. Women with unintended pregnancies tended to be younger, single and born in Canada compared to women with planned pregnancies. To support the second prong of the strategy to eliminate HIV infections in children, we need to improve on the integration between services for sexual and reproductive health and rights and services for women living with HIV.

Once women living with HIV are pregnant, the focus shifts to the third and fourth prong – preventing transmission to the infant and keeping the mother and infant healthy. Option B+ has transformed the approach in most antenatal clinics with high rates of coverage of HIV testing and most women receiving ART during pregnancy. In the One Stop Clinic in Ifakara, Tanzania, Gamell et al. show that almost all pregnant women, who do not already know that they are living with HIV, are offered an HIV test and that 94% accept it. Retesting late in pregnancy is not yet routine, and only 3% were re-tested, of whom one (2%) had seroconverted. Since acute HIV infection has such an important impact on the risk of transmission, re-testing later in pregnancy is now routine in many countries. Coverage is far from complete, so it is not always clear whether the high rates of seroconversion observed reflect a selection bias in choosing women who are at particularly high risk. This is an important area for research if we are to continue to drive down the already low transmission rates. Similarly the authors found that women who slipped through the net and presented in labour, were not always tested and did have a higher prevalence of infection - 5.2% vs. 3.1%. The other significant finding in Ifakara was that, as in many cohort studies, women were happy to take ART during pregnancy to protect their infants, but retention in care thereafter was much less impressive. Of

women newly diagnosed with HIV infection during pregnancy, 27% were lost to follow up at the time of the analysis.

Chadambuka et al. used qualitative methods to understand what impact the shift to option B+ has had in their study area in Zimbabwe. Overall, the women interviewed were very positive about treatment. They believed that it was good for their babies and also good for them, making them look healthy and thus avoiding stigma. However, women pointed out that their male partners are not exposed to as much information at the clinic or in the community. As a result, many men are less keen to be tested and sometimes not keen for their partners to be taking medicine despite appearing healthy. As one woman put it: "Very few men are supportive. You have to be strong. The men base their judgment on how healthy you appear to be as you carry yourself around and he also compares to how healthy he feels and opts to delay testing. But delaying only brings further harm. So when those men tell you to stop taking your medication, you need to tell them that they can stop if they want to, whilst you continue with your treatment." Within the power dynamics of many relationships, such a forthright approach may not be easy for all women. So we need continued attention on how to engage men in the process and how to empower women to act as agents of change within their communities.

Fertility intentions and contraceptive practices among clinic-users living with HIV in Kenya: a mixed methods study

Mayhew SH, Colombini M, Kimani JK, Tomlin K, Warren CE; Integra Initiative, Mutemwa R. BMC Public Health. 2017 Jul 5;17(1):626. doi: 10.1186/s12889-017-4514-2.

Background: Preventing unwanted pregnancies in Women Living with HIV (WLHIV) is a recognised HIV-prevention strategy. **This study explores the fertility intentions and contraceptive practices of WLHIV using services in Kenya**.

Methods: **Two hundred forty women self-identifying as WLHIV who attended reproductive health services in Kenya were interviewed with a structured questionnaire in 2011; 48 were also interviewed in-depth. STATA SE/13.1, Nvivo 8 and thematic analysis were used**.

Results: **Seventy one percent participants did not want another child; this was associated with having at least two living children and being the bread-winner**. **FP use was high (92%) but so were unintended pregnancies (40%) while living with HIV. 56 women reported becoming pregnant "while using FP": all were using condoms or short-term methods**. Only 16% participants used effective long-acting reversible contraceptives or permanent methods (LARC-PM). **Being older than 25 years and separated, widowed or divorced were significant predictors of long-term method use**. Qualitative data revealed strong motivation among WLHIV to plan or prevent pregnancies to avoid negative health consequences. Few participants received good information about contraceptive choices.

Conclusions: **WLHIV need better access to FP advice and a wider range of contraceptives including LARC to enable informed choices that will protect their fertility intentions, ensure planned pregnancies and promote safe child-bearing**.

Abstract Full-text [free] access

Contraceptive use and unplanned pregnancy among female sex workers in Zambia

Chanda MM, Ortblad KF, Mwale M, Chongo S, Kanchele C, Kamungoma N, Barresi LG, Harling G, Bärnighausen T, Oldenburg CE. Contraception. 2017 Sep;96(3):196-202. doi: 10.1016/j.contraception.2017.07.003. Epub 2017 Jul 12.

Objectives: Access to reproductive healthcare, including contraceptive services, is an essential component of comprehensive healthcare for female sex workers (FSW). Here, **we evaluated the prevalence of and factors associated with contraceptive use, unplanned pregnancy, and pregnancy termination among FSW in three transit towns in Zambia.**

Study design: **Data arose from the baseline quantitative survey from a randomized controlled trial of HIV self-testing among FSW**. Eligible **participants were 18 years of age or older, exchanged sex for money or goods at least once in the past month, and were HIV-uninfected or status unknown without recent HIV testing (<3 months).** Logistic regression models were used to assess factors associated with contraceptive use and unplanned pregnancy.

Results: **Of 946 women eligible for this analysis, 84.1% had been pregnant at least once, and among those 61.6% had an unplanned pregnancy, and 47.7% had a terminated pregnancy**. **Incarceration was associated with decreased odds of dual contraception use** (aOR=0.46, 95% CI 0.32-0.67) **and increased odds of unplanned pregnancy** (aOR=1.75, 95% CI 1.56-1.97). **Condom availability at work was associated with increased odds of using condoms only for contraception** (aOR=1.74, 95% CI 1.21-2.51) **and decreased odds of unplanned pregnancy** (aOR=0.63, 95% CI 0.61-0.64).

Conclusions: **FSW in this setting have large unmet reproductive health needs**. Structural interventions, such as increasing condom availability in workplaces, may be useful for reducing the burden of unplanned pregnancy.

Abstract Full-text [free] access

Pregnancy incidence and intention after HIV diagnosis among women living with HIV in Canada

Salters K, Loutfy M, de Pokomandy A, Money D, Pick N, Wang L, Jabbari S, Carter A, Webster K, Conway T, Dubuc D, O'Brien N, Proulx-Boucher K, Kaida A; CHIWOS Research Team. PLoS One. 2017 Jul 20;12(7):e0180524. doi: 10.1371/journal.pone.0180524. eCollection 2017.

Background: Pregnancy incidence rates among women living with HIV (WLWH) have increased over time due to longer life expectancy, improved health status, and improved access to and HIV prevention benefits of combination antiretroviral therapy (cART). However, it is unclear whether intended or unintended pregnancies are contributing to observed increases.

Methods: **We analyzed retrospective data from the Canadian HIV Women's Sexual and Reproductive Health Cohort Study** (CHIWOS). **Kaplan-Meier methods and GEE Poisson models were used to measure cumulative incidence and incidence rate of pregnancy after HIV diagnosis overall, and by pregnancy intention.** We used multivariable logistic regression models to examine independent correlates of unintended pregnancy among the most recent/current pregnancy.

Results: **Of 1165 WLWH included in this analysis, 278** (23.9%) **women reported 492 pregnancies after HIV diagnosis, 60.8% of which were unintended**. **Unintended pregnancy incidence** (24.6 per 1000 women-years (WYs); 95% CI: 21.0, 28.7) **was higher than intended pregnancy incidence** (16.6 per 1000 WYs; 95% CI: 13.8, 20.1) (Rate Ratio: 1.5, 95% CI: 1.2-1.8). **Pregnancy incidence among WLWH who initiated cART before or during pregnancy** (29.1 per 1000 WYs with 95% CI: 25.1, 33.8) **was higher than among WLWH not on cART during pregnancy** (11.9 per 1000 WYs; 95% CI: 9.5, 14.9) (Rate Ratio: 2.4, 95% CI: 2.0-3.0). **Women with current or recent unintended pregnancy** (vs. intended pregnancy) **had higher adjusted odds of being single** (AOR: 1.94; 95% CI: 1.10, 3.42), **younger at time of conception** (AOR: 0.95 per year increase, 95% CI: 0.90, 0.99), **and being born in Canada** (AOR: 2.76, 95% CI: 1.55, 4.92).

Conclusion: **Nearly one-quarter of women reported pregnancy after HIV diagnosis, with 61% of all pregnancies reported as unintended.** Integrated HIV and reproductive health care programming is required to better support WLWH to optimize pregnancy planning and outcomes and to prevent unintended pregnancy.

Abstract Full-text [free] access

Prevention of mother-to-child transmission of HIV Option B+ cascade in rural Tanzania: the One Stop Clinic model

Gamell A, Luwanda LB, Kalinjuma AV, Samson L, Ntamatungiro AJ, Weisser M, Gingo W, Tanner M, Hatz C, Letang E, Battegay M; KIULARCO Study Group. PLoS One. 2017 Jul 12;12(7):e0181096. doi: 10.1371/journal.pone.0181096. eCollection 2017.

Background: Strategies to improve the uptake of Prevention of Mother-To-Child Transmission of HIV (PMTCT) are needed. **We integrated HIV and maternal, newborn and child health services in a One Stop Clinic to improve the PMTCT cascade in a rural Tanzanian setting**.

Methods: The One Stop Clinic of Ifakara offers integral care to HIV-infected pregnant women and their families at one single place and time. **All pregnant women and HIV-exposed infants attended during the first year of Option B+ implementation** (04/2014-03/2015) **were included**. **PMTCT was assessed at the antenatal clinic** (ANC), **HIV care and labour ward, and compared with the pre-B+ period.** We also characterised HIV-infected pregnant women and evaluated the MTCT rate.

Results: **1579 women attended the ANC. Seven** (0.4%) **were known to be HIV-infected**. **Of the remainder, 98.5%** (1548/1572) **were offered an HIV test**, **94%** (1456/1548) **accepted and 38** (2.6%) **tested HIV-positive**. **51 were re-screened for HIV during late pregnancy and one had seroconverted**. **The HIV prevalence at the ANC was 3.1%** (46/1463). **Of the 39 newly diagnosed women, 35** (90%) **were linked to care**. HIV test was offered to >98% of ANC clients during both the pre- and post-B+ periods. **During the post-B+ period, test acceptance** (94% versus 90.5%, p<0.0001) **and linkage to care** (90% versus 26%, p<0.0001) **increased**. **Ten additional women diagnosed outside the ANC were linked to care**. 82% (37/45) of these newly-enrolled women started antiretroviral treatment (ART). After a median time of 17 months, 27% (12/45) were lost to follow-up. 79 women under HIV care became pregnant and all received ART. After a median follow-up time of 19 months, 6% (5/79) had been lost. 5727 women delivered at the hospital, 20% (1155/5727) had unknown HIV serostatus. Of these, 30% (345/1155) were tested for HIV, and 18/345 (5.2%) were HIV-positive. **Compared to the pre-B+ period more women were tested during labour** (30% versus 2.4%, p<0.0001). **During the study, the MTCT rate was 2.2%**.

Conclusions: **The implementation of Option B+ through an integrated service delivery model resulted in universal HIV testing in the ANC, high rates of linkage to care, and MTCT below the elimination threshold**. However, **HIV testing in late pregnancy and labour, and retention during early ART need to be improved.**

Abstract Full-text [free] access

Acceptability of lifelong treatment among HIV-positive pregnant and breastfeeding women (Option B+) in selected health facilities in Zimbabwe: a qualitative study

Chadambuka A, Katirayi L, Muchedzi A, Tumbare E, Musarandega R, Mahomva AI, Woelk G BMC Public Health. 2017 Jul 25;18(1):57. doi: 10.1186/s12889-017-4611-2.

Background: Zimbabwe's Ministry of Health and Child Care (MOHCC) adopted 2013 World Health Organization (WHO) prevention of mother-to-child HIV transmission (PMTCT) guidelines recommending initiation of HIV-positive pregnant and breastfeeding women (PPBW) on lifelong antiretroviral treatment (ART) irrespective of clinical stage (Option B+). Option B+ was officially launched in Zimbabwe in November 2013; however the acceptability of life-long ART and its potential uptake among women was not known.

Methods: **A qualitative study was conducted at selected sites in Harare (urban) and Zvimba (rural) to explore Option B+ acceptability; barriers, and facilitators to ART adherence and service uptake. In-depth interviews (IDIs), focus group discussions (FGDs) and key informant interviews (KIIs) were conducted with PPBW, healthcare providers, and community members.** All interviews were audio-recorded, transcribed, and translated; data were coded and analyzed in MaxQDA v10.

Results: **Forty-three IDIs, 22 FGDs, and five KIIs were conducted. The majority of women accepted lifelong ART. There was however, a fear of commitment to taking lifelong medication because they were afraid of defaulting, especially after cessation of breastfeeding**. There was confusion around dosage; and fear of side effects, not having enough food to take drugs, and the lack of opportunities to ask questions in counseling. **Participants reported the need for strengthening community sensitization for Option B+. Facilitators included receiving a simplified pill regimen; ability to continue breastfeeding beyond 6 months like HIV-negative women; and partner, community and health worker support. Barriers included distance of health facility, non-disclosure of HIV status, poor male partner support and knowing someone who had negative experience on ART**.

Conclusions: **This study found that Option B+ is generally accepted among PPBW as a means to strengthen their health and protect their babies**. Consistent with previous literature, **this study demonstrated the importance of male partner and community support in satisfactory adherence to ART and enhancing counseling techniques.** Strengthening community sensitization and male knowledge is critical to encourage women to disclose their HIV status and ensure successful adherence to ART. Targeting and engaging partners of women will remain key determinants to women's acceptance and adherence on ART under Option B+

Abstract Full-text [free] access

3. Combination prevention

HIV risk – where do perception and reality overlap?

Editor's notes: *Whereas pregnancy occurs quite frequently after unprotected sex, as discussed in the previous commentary, HIV is not transmitted so easily. In their guidance on PrEP in 2015, WHO refers to substantial risk at a level of around 3% per year, which of course means that 97% of people in that risk group do not become HIV-positive in that year. However, risk can only be measured at a group level. Not only does this mean that there may be unrecognized risk factors, but also at the individual level we seldom calculate a mathematical risk of something happening to us. So a better understanding of how people perceive their risk and how this relates to their actual likelihood of becoming HIV-positive is important for many aspects of HIV prevention and behaviour change communication. Among gay men and other men who have sex with men in Europe, Australia and the US, self-identification, combined with a few screening questions could distinguish men at very high*

risk for whom PrEP is an obvious choice. Adherence in this group tends to be good and the benefits far outweigh the costs, both financial and other.

In other populations, the equation is not so straightforward. People at lower risk of HIV may still choose to take PrEP (or use other prevention technologies in the future) but the financial costs of preventing new HIV infections will always be higher for people who adhere less and are at lower risk. Two papers this month consider aspects of this question. Haberer et al. considered the overlap between PrEP adherence and risky periods within the Partners Demonstration Project, in Kenya and Uganda. In this project, serodiscordant couples were recruited and offered PrEP if they met criteria that showed that the seronegative partner had a risk of seroconversion modelled at three to four percent per year. Thus the seronegative population as a whole was at substantial risk. The authors then further classified those periods where the HIV-positive participant had not yet had six months of ART and the couple had not used condoms all the time as high risk. Prevention-effective adherence was defined as taking sufficient PrEP tablets to be effective during the periods when sex could be considered high risk. The authors found that, reassuringly, during 75% of the time periods in their study, participants should have been protected. This helps to explain the overall high effectiveness observed in the study and suggests that in this context people make rational decisions about when to adhere to their PrEP and when they do not need to worry so much.

The study contrasts somewhat with a study from South Africa by Maughan-Brown and Venkataramani. The authors were able to use some of the most detailed information to have been collected on perceived risk of HIV infection among participants in the Cape Area Panel Study which ran from 2002 – 2009. Detailed questionnaires on risk perception and behaviours were collected in successive surveys. In the final survey in 2009, HIV testing was included which allowed the authors to test whether perception of risk translated into HIV seroconversion. Their conclusions are that perception of risk did NOT translate into actual risk. They acknowledge that perceptions may have changed over the ensuing years but it is a cautionary study that challenges our assumptions that people who consider themselves at risk are the most likely beneficiaries of prevention efforts. On the other hand, it is impossible to offer prevention technology to people who do not consider themselves at risk. The challenge is to find communication and delivery systems that will encourage the perfect combination of people who are genuinely at risk, people who want to use the technology and people who will adhere to it faithfully. A key determinant remains the costs. Focusing on this perfect combination maximizes the cost-effectiveness of prevention technologies, but that should not preclude allowing people who want to use it to do so at their own cost.

Some potential technologies are still very expensive. Infusions of broadly neutralizing antibodies are being tested in the Antibody Mediated Prevention (AMP) study in order to define the level and duration of protection of such a strategy. This will help design future vaccine strategies or could be used for specific protection needs if the cost of antibody production falls. So, the study from Sok et al. is exciting if still a long way from the field. Until now, generating broadly neutralizing antibodies in the laboratory has proved challenging. Standard approaches require multiple sequential immunogens to be administered to drive the antibody maturation process in rabbits or macaques, followed by purification of the relevant monoclonal antibody. However, cows have a rather different antibody configuration, and in this study, four cows developed useful cross-clade coverage after regular boosts with just a single immunogen. Of particular interest was the fact that the antibody response continued to evolve so that the later antibodies showed broader activity, despite no additional immunogens. During the Paris IAS HIV Science conference, Dr Fauci foresaw a future where people living with HIV might be maintained in long-term remission without ART by regular doses of powerful antibodies possibly given subcutaneously. Science fiction or a realistic avenue?

Finally, we need to remember that some risk factors for HIV transmission are only just being elucidated. There has been considerable interest in the vaginal microbiome. Women whose vaginas are largely colonized by lactobacilli are less likely to become HIV-positive, whereas women with bacterial vaginosis, or dysbiosis are more likely to. Liu et al. have study the microbiome of the foreskin in uncircumcised men in the control arm of one of the large randomized trials of voluntary medical male circumcision in Uganda. The authors show that men in whom they could demonstrate bacterial species such as prevotella, dialister, finegoldia, and peptoniphilus were significantly more likely to become HIV-positive on follow up than men who did not have these anaerobic microorganisms. Furthermore, they point out that these same bacteria can be passed on to the woman, where they may also cause colonization and thus transmit an increased susceptibility to the female partner too. The challenge is that while a simple course of antibiotics may kill the relevant organisms in both men and women, recurrence is common. Microbiomes are an essential part of sexual and reproductive health. Another up and coming area for research.

Alignment of adherence and risk for HIV acquisition in a demonstration project of pre-exposure prophylaxis among HIV serodiscordant couples in Kenya and Uganda: a prospective analysis of prevention-effective adherence.

Haberer JE, Kidoguchi L, Heffron R, Mugo N, Bukusi E, Katabira E, Asiimwe S, Thomas KK, Celum C, Baeten JM. J Int AIDS Soc. 2017 Jul 25;20(1):1-9. doi: 10.7448/IAS.20.1.21842.

Introduction: Adherence is essential for pre-exposure prophylaxis (PrEP) to protect against HIV acquisition, but PrEP use need not be life-long. **PrEP is most efficient when its use is aligned with periods of risk - a concept termed prevention-effective adherence. The objective of this paper is to describe prevention-effective adherence and predictors of adherence within an open-label delivery project of integrated PrEP and antiretroviral therapy (ART) among HIV serodiscordant couples in Kenya and Uganda (the Partners Demonstration Project)**.

Methods: **We offered PrEP to HIV-uninfected participants until the partner living with HIV had taken ART for ≥6 months** (a strategy known as "**PrEP as a bridge to ART**"). The level of adherence sufficient to protect against HIV was estimated in two ways: ≥4 and ≥6 doses/week (per electronic monitoring). **Risk for HIV acquisition was considered high if the couple reported sex with <100% condom use before six months of ART, low if they reported sex but had 100% condom use and/or six months of ART and very low if no sex was reported**. We assessed prevention-effective adherence by cross-tabulating PrEP use with HIV risk and used multivariable regression models to assess predictors of ≥4 and ≥6 doses/week.

Results: **A total of 985 HIV-uninfected participants initiated PrEP; 67% were male, median age was twenty-nine years, and 67% reported condomless sex in the month before enrolment**. An average of ≥4 doses and ≥6 doses/week were taken in 81% and 67% of participant-visits, respectively. **Adherence sufficient to protect against HIV acquisition was achieved in 75-88% of participant-visits with high HIV risk**. **The strongest predictor of achieving sufficient adherence was reporting sex with the study partner who was living with HIV**; other statistically significant predictors included no concerns about daily PrEP, pregnancy or pregnancy intention, females aged >25 years, older male partners and desire for relationship success. **Predictors of not achieving sufficient adherence were no longer being a couple, delayed PrEP initiation, >6 months of follow-up, ART use >6 months by the partner living with HIV and problem alcohol use**.

Conclusions: **Over three-quarters of participant-visits by HIV-uninfected partners in serodiscordant couples achieved prevention-effective adherence with PrEP**. Greater adherence

was observed during months with HIV risk and the strongest predictor of achieving sufficient adherence was sexual activity.

Abstract Full-text [free] access

Accuracy and determinants of perceived HIV risk among young women in South Africa.

Maughan-Brown B, Venkataramani AS. BMC Public Health. 2017 Jul 21;18(1):42. doi: 10.1186/s12889-017-4593-0.

Background: HIV risk perceptions are a key determinant of HIV testing. The success of efforts to achieve an AIDS-free generation - including reaching the UNAIDS 90-90-90 target - thus depends critically on the content of these perceptions. **We examined the accuracy of HIV-risk perceptions and their correlates among young black women in South Africa**, a group with one of the highest HIV incidence rates worldwide.

Methods: **We used individual-level longitudinal data from the Cape Area Panel Study (CAPS) from 2005 to 2009 on black African women (20-30 years old in 2009) to assess the association between perceived HIV-risk in 2005 and the probability of testing HIV-positive four years later**. We then estimated multivariable logistic regressions using cross-sectional data from the 2009 CAPS wave to assess the relationship between risk perceptions and a wide range of demographic, sexual behaviour and psychosocial covariates of perceived HIV-risk.

Results: **We found that the proportion testing HIV-positive in 2009 was almost identical across perceived risk categories in 2005** (no, small, moderate, great) (χ 2 = 1.43, p = 0.85**). Consistent with epidemiologic risk factors, the likelihood of reporting moderate or great HIV-risk perceptions was associated with condom-use** (aOR: 0.57; 95% CI: 0.36, 0.89; p < 0.01); **having ≥3 lifetime partners** (aOR: 2.38, 95% CI: 1.53, 3.73; p < 0.01); **knowledge of one's partner's HIV status** (aOR: 0.67; 95% CI: 0.43, 1.07; p = 0.09); **and being in an age-disparate partnership** (aOR: 1.73; 95% CI: 1.09, 2.76; p = 0.02). However, the likelihood of reporting moderate or great self-perceived risk did not vary with sexually transmitted disease history and respondent age, both strong predictors of HIV risk in the study setting. **Risk perceptions were associated with stigmatising attitudes** (aOR: 0.53; 95% CI: 0.26, 1.09; p = 0.09); **prior HIV testing** (aOR: 0.21; 95% CI: 0.13, 0.35; p < 0.01); **and having heard that male circumcision is protective** (aOR: 0.38; 95% CI: 0.22, 0.64; p < 0.01).

Conclusions: **Results indicate that HIV-risk perceptions are inaccurate. Our findings suggest that this inaccuracy stems from HIV-risk perceptions being driven by an incomplete understanding of epidemiological risk and being influenced by a range of psycho-social factors not directly related to sexual behaviour**. Consequently, new interventions are needed to align perceived and actual HIV risk.

Abstract Full-text [free] access

Rapid elicitation of broadly neutralizing antibodies to HIV by immunization in cows.

Sok D, Le KM, Vadnais M, Saye-Francisco KL, Jardine JG, Torres JL, Berndsen ZT, Kong L, Stanfield R, Ruiz J, Ramos A, Liang CH, Chen PL, Criscitiello MF, Mwangi W, Wilson IA, Ward AB, Smider VV, Burton DR. Nature. 2017 Aug 3;548(7665):108-111. doi: 10.1038/nature23301. Epub 2017 Jul 20.

No immunogen to date has reliably elicited broadly neutralizing antibodies to HIV in humans or animal models. **Advances in the design of immunogens that antigenically mimic the HIV envelope glycoprotein (Env), such as the soluble cleaved trimer BG505 SOSIP, have improved the elicitation of potent isolate-specific antibody responses in rabbits and macaques, but so far failed to induce broadly neutralizing antibodies**. One possible reason for this failure is that the relevant antibody repertoires are poorly suited to target the conserved epitope regions on Env, which are somewhat occluded relative to the exposed variable epitopes. **Here, to test this hypothesis, we immunized four cows with BG505 SOSIP. The antibody repertoire of cows contains long third heavy chain complementary determining regions (HCDR3) with an ultralong subset that can reach more than 70 amino acids in length. Remarkably, BG505 SOSIP immunization resulted in rapid elicitation of broad and potent serum antibody responses in all four cows.** Longitudinal serum analysis for one cow showed the development of neutralization breadth (20%, n = 117 cross-clade isolates) in 42 days and 96% breadth (n = 117) at 381 days. A monoclonal antibody isolated from this cow harboured an ultralong HCDR3 of 60 amino acids and neutralized 72% of cross-clade isolates (n = 117) with a potent median IC50 of 0.028 μg ml-1. Breadth was elicited with a single trimer immunogen and did not require additional envelope diversity**. Immunization of cows may provide an avenue to rapidly generate antibody prophylactics and therapeutics to address disease agents that have evolved to avoid human antibody responses.**

Abstract access

Penile anaerobic dysbiosis as a risk factor for HIV infection.

Liu CM, Prodger JL, Tobian AAR, Abraham AG, Kigozi G, Hungate BA, Aziz M, Nalugoda F, Sariya S, Serwadda D, Kaul R, Gray RH, Price LB. MBio. 2017 Jul 25;8(4). pii: e00996-17. doi: 10.1128/mBio.00996-17.

Sexual transmission of HIV requires exposure to the virus and infection of activated mucosal immune cells, specifically CD4+ T cells or dendritic cells. The foreskin is a major site of viral entry in heterosexual transmission of HIV. Although the probability of acquiring HIV from a sexual encounter is low, the risk varies even after adjusting for known HIV risk factors. The genital microbiome may account for some of the variability in risk by interacting with the host immune system to trigger inflammatory responses that mediate the infection of mucosal immune cells. **We conducted a case-control study of uncircumcised participants nested within a randomized-controlled trial of male circumcision in Rakai, Uganda. Using penile (coronal sulcus) swabs collected by study personnel at trial enrollment, we characterized the penile microbiome by sequencing and real-time PCR and cytokine levels by electrochemiluminescence assays. The absolute abundances of penile anaerobes at enrollment were associated with later risk of HIV seroconversion, with a 10-fold increase in Prevotella, Dialister, Finegoldia, and Peptoniphilus increasing the odds of HIV acquisition by 54 to 63%, after controlling for other known HIV risk factors.** Increased abundances of anaerobic bacteria were also correlated with increased cytokines, including interleukin-8, which can trigger an inflammatory response that recruits susceptible immune cells, suggesting a mechanism underlying the increased risk**. These same anaerobic genera can be shared between heterosexual partners and are associated with increased HIV acquisition in women, pointing to anaerobic dysbiosis in the genital microbiome and an accompanying inflammatory response as a novel, independent, and transmissible risk factor for HIV infection**.

Importance: **We found that uncircumcised men who became infected by HIV during a 2-year clinical trial had higher levels of penile anaerobes than uncircumcised men who remained HIV negative. We also found that having higher levels of penile anaerobes was also associated**

with higher production of immune factors that recruit HIV target cells to the foreskin, suggesting that anaerobes may modify HIV risk by triggering inflammation. These anaerobes are known to be shared by heterosexual partners and are associated with HIV risk in women. **Therefore, penile anaerobes may be a sexually transmissible risk factor for HIV, and modifying the penile microbiome could potentially reduce HIV acquisition in both men and women**.

Abstract Full-text [free] access

4. Elimination of gender inequalities

How to enhance adolescents' autonomy and self-esteem. Cash and schooling help

Editor's notes: *Recent randomized trials of interventions including cash transfers to adolescent girls to encourage school attendance in South Africa have failed to show an effect on the incidence of HIV or pregnancy and had mixed effects on the incidence of HSV2. However, these large trials both found that school attendance was rather high in the study populations possibly limiting the opportunities for making an impact on HIV. McPhail et al. now report an interesting study that explores what the young women chose to spend their cash on; who controlled the cash and whether there were adverse consequences of giving cash to dependents rather than to the household or its head. This is important because some studies elsewhere have suggested that such payments might upset the family dynamic and introduce tensions. In this relatively poor South African setting (which is still considerably less poor than many other communities in neighbouring countries), the authors found minimal harms and many benefits. Women used the money to express their autonomy and to build their status among their peers and community. Money was not wasted on drugs and alcohol that might increase risks of HIV, although it was also not spent on condoms or family planning services (which are anyway provided to some extent at no cost in this community). Although the HPTN 068 randomised trial in which the study was embedded did not show any impact on the primary and secondary biological endpoints (incidence of HIV, HSV2 and pregnancy), the benefits described in terms of adolescent development are important in their own right. Cash transfers for people near the poverty line and keeping girls in school probably have many complex and important benefits beyond HIV prevention.*

Improving school attendance and integrating reproductive health or HIV prevention into the curriculum feels as though it should be an essential part of HIV programming. Yet, several large well-designed studies have failed to demonstrate significant effects on HIV incidence, pregnancy or other biological markers. Hallfors et al. have examined one such negative trial in more detail. They show that in the trial in Kenya where orphaned children were supported with uniforms, school fees and regular nurse visits, it appeared that the intervention did lead to a higher attendance at school. However, this did not translate into differences in the biological markers chosen for the endpoints of the trial. The authors comment that "the association between school support and HIV/HSV-2 prevention appears to be weak or under-specified". However, as with the cash transfers, the benefits may be much broader than changes in the biological endpoints specified. Furthermore, it is plausible that a stronger educational input may eventually translate into HIV-relevant outcomes beyond the timeframe of the study. Trials in these areas are hard to design. We do need to build a stronger case for the real impact on HIV of different aspects of schooling both in terms of quantity and of quality. But that should not detract from the obvious benefits of investing in better education for all.

Cash transfers for HIV prevention: what do young women spend it on? Mixed methods findings from HPTN 068.

MacPhail C, Khoza N, Selin A, Julien A, Twine R, Wagner RG, Goméz-Olivé X, Kahn K, Wang J, Pettifor A. BMC Public Health. 2017 Jul 11;18(1):10. doi: 10.1186/s12889-017-4513-3.

Background: Social grants have been found to have an impact on health and wellbeing in multiple settings. Who receives the grant, however, has been the subject of discussion with regards to how the money is spent and who benefits from the grant.

Methods: **Using survey data from 1214 young women who were in the intervention arm and completed at least one annual visit in the HPTN 068 trial, and qualitative interview data from a subset of 38 participants, we examined spending of a cash transfer provided to young women conditioned on school attendance**.

Results: **We found that spending was largely determined and controlled by young women themselves and that the cash transfer was predominately spent on toiletries, clothing and school supplies. In interview data, young women discussed the significant role of cash transfers for adolescent identity, specifically with regard to independence from family and status within the peer network.** There were almost no negative consequences from receiving the cash transfer.

Conclusions: **We established that providing adolescents access to cash was not reported to be associated with social harms or negative consequences. Rather, spending of the cash facilitated appropriate adolescent developmental behaviours**. The findings are encouraging at a time in which there is global interest in addressing the structural drivers of HIV risk, such as poverty, for young women.

Abstract Full-text [free] access

Process evaluation of a clinical trial to test school support as HIV prevention among orphaned adolescents in western Kenya.

Hallfors DD, Cho H, Hartman S, Mbai I, Ouma CA, Halpern CT. Prev Sci. 2017 Jul 21. doi: 10.1007/s11121-017-0827-8. [Epub ahead of print]

Orphaned adolescents are a large and vulnerable population in sub-Saharan Africa, at higher risk for HIV than non-orphans. Yet prevention of new infection is critical for adolescents since they are less likely than adults to enter and remain in treatment and are the only age group with rising AIDS death rates. **We report process evaluation for a randomized controlled trial (RCT) testing support to stay in school (tuition, uniform, nurse visits) as an HIV prevention strategy for orphaned Kenyan adolescents**. **The RCT found no intervention effect on HIV/HSV-2 biomarker outcomes**. With process evaluation, we examined the extent to which intervention elements were implemented as intended among the intervention group (N = 412) over the 3-year study period (2012-2014), the implementation effects on school enrollment (0-9 terms), and whether more time in school impacted HIV/HSV-2. All analyses examined differences as a whole, and by gender. Findings indicate that school fees and uniforms were fully implemented in 94 and 96% of cases, respectively. On average, participants received 79% of the required nurse visits. Although better implementation of nurse visits predicted more terms in school, a number of terms did not predict the likelihood of HIV/HSV-2 infection. Attending boarding school also increased number of school terms, but reduced the odds of infection for boys only. **Four previous RCTs have been conducted in sub-Saharan Africa, and only one found limited evidence of school impact on adolescent HIV/HSV-2**

infection. Our findings add further indication that the association between school support and HIV/HSV-2 prevention appears to be weak or under-specified.

Abstract access

5. Health systems and services

Understanding different levels and different models of integration

Editor's notes: *Integration between HIV services and programmes and other services and programmes sounds like common sense. As people with HIV live longer they are more likely to develop other chronic conditions. Some of these conditions may also be exacerbated by some anti-retroviral medicines, although modern treatment regimens have much less effect on lipid and insulin metabolism. Low grade chronic inflammation may continue even in people whose HIV is suppressed and people whose CD4 count sunk to a low level before starting seem to be at greater risk of subsequent cardiovascular disease. Then there are diseases that are more common among people living with HIV, such as tuberculosis and invasive cervical cancer. And HIV programmes around the world have established some of the best clinical services for chronic care, with regular appointments, decentralized follow-up, algorithmic approaches to clinical changes and so on. So it seems sensible to look for the synergies and build on them.*

However, research on integration makes it clear that there are many different interpretations of what integration should or could mean. In different epidemiological settings, the priorities will inevitably be very different. Two useful systematic reviews this month by the same team, review this territory for cardiovascular diseases, diabetes and cervical cancer.

Haldane et al. distinguish between the levels of integration. Micro level integration involves direct patient care and adjusting diagnosis, treatment and support appropriately. Meso level integration refers to changes made at the clinic or delivery system level, while macro level integration is about programme management, supply chains and systems organisation. Despite a large literature (over 7600 papers) on the overlaps between HIV and cardiovascular diseases and diabetes, the authors found only 14 studies that allowed aspects of the integration to be assessed, and only one of these evaluated outcomes. The others were descriptive studies which highlighted many innovative models, almost all at the meso-level.

Similarly for invasive cervical cancer, which is at least four times as common among women living with HIV as seronegative women, Sigfrid et al. found many papers but only 21 that met their inclusion criteria. Their models of integration could all be said to be at the meso-level, with one stop shops; co-located services or more complex integrated pathways described. Again, there were no good evaluations of the outcomes of these systematic changes to the way that services are delivered. In most countries, all women with cervical cancer should at least be offered an HIV test and appropriate linkage to care expedited for those found to be seropositive. Women living with HIV need regular screening for early cervical cancer and (as discussed last month) screening for human papillomavirus, the underlying cause of cervical cancer. However, many ART clinics are now busy and crowded so that even if staff are trained, they do not have time or space or privacy to do cervical examinations. HPV vaccination campaigns need to be carried out in schools before girls become sexually active. This could be a good time to engage with sexuality education. However, many campaigns have tended to avoid the challenges of discussing sex with girls who are not yet sexually active, preferring to focus on the vaccine as a cancer prevention tool. So, the lesson from both these papers is that we

need to define more rigorously what we want to achieve with integration and then ensure that we evaluate whether or not our interventions achieve it.

Tuberculosis and HIV have been dancing together since the first descriptions of HIV in the 1980s. The large majority of tuberculosis patients in many countries are now screened for HIV, with appropriate referral and increasing numbers of people living with HIV are screened regularly for the four classic symptoms of tuberculosis (weight loss, cough, night sweats and fever) and referred onwards for diagnosis. Yet we still find that collaboration between programmes is not always easy. The number of people living with HIV who are also on tuberculosis treatment reported by the HIV programme may not be the same as the number of people on tuberculosis treatment who are also living with HIV reported by the tuberculosis programme. Osei et al. report from the Volta Region of Ghana that more than 90% of tuberculosis patients had an HIV test recorded in the tuberculosis register, with an HIV prevalence of 18%. As has been reported frequently elsewhere, the authors found that HIV was commoner in those with smear negative tuberculosis, and the outcome of treatment was less good. Their recommendation for strengthening the collaboration between tuberculosis and HIV makes sense, although it has been WHO policy for many years.

The WHO guidance on collaborative TB/HIV activities has always included isoniazid preventive therapy. However, this remains poorly implemented for reasons that are never very clear. Despite no good evidence, many tuberculosis programme staff and clinicians worry about the risk of generating isoniazid resistant tuberculosis. Many HIV programme staff feel that isoniazid remains in the realm of the tuberculosis programme, so that although they are happy to promote cotrimoxazole, they are much slower to prescribe isoniazid. Many also feel that ART alone should be sufficient to prevent tuberculosis, despite randomized trials in high prevalence settings that demonstrate the additional benefits of isoniazid. Shayo et al. make a strong economic argument for promoting isoniazid in their study in Tanzania. They base their model on the rates of tuberculosis and mortality seen during the expansion of pilot programmes for isoniazid in Dar es Salaam. Both tuberculosis and mortality were significantly lower in the clinics which were part of the pilot programme. In fact, mortality was approximately tenfold lower, which seems unlikely to be simply due to isoniazid. Some studies such as TEMPRANO have shown a mortality benefit from isoniazid, while many trials have failed to do so. Given the non-randomized nature of the comparison, the authors do point out that their conclusions must be tentative. Nonetheless, it is a convincing demonstration that isoniazid preventive therapy can be incorporated into a busy HIV care clinic and there is abundant evidence that this is the right thing to do.

One more tuberculosis study this month was carried out in Germany. Karo et al. reviewed the immunology of the 139 people who developed tuberculosis among more than 10 000 people living with HIV in the German ClinSurv cohort. The authors excluded people who already had tuberculosis at the time that HIV was diagnosed, and found that new diagnoses of tuberculosis were most common in the first couple of years after starting ART. The authors also show that immune restoration was slower in people who developed tuberculosis. There was still some deficit up to seven years after ART was started. Again, their conclusion is that we should be using isoniazid to prevent tuberculosis in people living with HIV, especially people who have spent much of their lives in areas of the world, such as sub-Saharan Africa where tuberculosis is much more prevalent than in Europe. It is often said that Mycobacterium tuberculosis is a very slow growing organism. We must work harder to ensure that our response to it is not very slow too. Tuberculosis remains the biggest killer of people with HIV in most of the world, yet for years we have known that a simple, cheap, non-toxic treatment can prevent it.

Integrating cardiovascular diseases, hypertension, and diabetes with HIV services: a systematic review.

Haldane V, Legido-Quigley H, Chuah FLH, Sigfrid L, Murphy G, Ong SE, Cervero-Liceras F, Watt N, Balabanova D, Hogarth S, Maimaris W, Buse K, McKee M, Piot P, Perel P. AIDS Care. 2017 Jul 5:1-13. doi:10.1080/09540121.2017.1344350. [Epub ahead of print]

Non-communicable diseases (NCDs), including cardiovascular diseases (CVD), hypertension and diabetes together with HIV infection are among the major public health concerns worldwide. Health services for HIV and NCDs require health systems that provide for people's chronic care needs, which present an opportunity to coordinate efforts and create synergies between programs to benefit people living with HIV and/or AIDS and NCDs. **This review included studies that reported service integration for HIV and/or AIDS with coronary heart diseases, chronic CVD, cerebrovascular diseases (stroke), hypertension or diabetes. We searched multiple databases from inception until October 2015.** Articles were screened independently by two reviewers and assessed for risk of bias. 11 057 records were identified with 7 616 after duplicate removal. **After screening titles and abstracts, 14 papers addressing 17 distinct interventions met the inclusion criteria**. **We categorized integration models by diseases** (HIV with diabetes, HIV with hypertension and diabetes, HIV with CVD and finally HIV with hypertension and CVD and diabetes). **Models also looked at integration from micro** (patient focused integration) **to macro** (system level integrations). **Most reported integration of hypertension and diabetes with HIV and AIDS services and described multidisciplinary collaboration, shared protocols, and incorporating screening activities into community campaigns. Integration took place exclusively at the meso-level, with no micro- or macro-level integrations described**. Most were descriptive studies, with one cohort study reporting evaluative outcomes. **Several innovative initiatives were identified and studies showed that CVD and HIV service integration is feasible**. **Integration should build on existing protocols and use the community as a locus for advocacy and health services, while promoting multidisciplinary teams, including greater involvement of pharmacists.** There is a need for robust and well-designed studies at all levels - particularly macro-level studies, research looking at long-term outcomes of integration, and research in a more diverse range of countries.

Abstract access

Integrating cervical cancer with HIV healthcare services: A systematic review.

Sigfrid L, Murphy G, Haldane V, Chuah FLH, Ong SE, Cervero-Liceras F, Watt N, Alvaro A, Otero-Garcia L, Balabanova D, Hogarth S, Maimaris W, Buse K, Mckee M, Piot P, Perel P, Legido-Quigley H. PLoS One. 2017 Jul 21;12(7):e0181156. doi: 10.1371/journal.pone.0181156. eCollection 2017.

Background: Cervical cancer is a major public health problem. Even though readily preventable, it is the fourth leading cause of death in women globally. Women living with HIV are at increased risk of invasive cervical cancer, highlighting the need for access to screening and treatment for this population. Integration of services has been proposed as an effective way of improving access to cervical cancer screening especially in areas of high HIV prevalence as well as lower resourced settings. **This paper presents the results of a systematic review of programs integrating cervical cancer and HIV services globally, including feasibility, acceptability, clinical outcomes and facilitators for service delivery.**

Methods: This is part of a larger systematic review on integration of services for HIV and non-communicable diseases. **To be considered for inclusion studies had to report on programs to**

integrate cervical cancer and HIV services at the level of service delivery. We searched multiple databases including Global Health, Medline and Embase from inception until December 2015. Articles were screened independently by two reviewers for inclusion and data were extracted and assessed for risk of bias.

Main results**: 11 057 records were identified initially. 7616 articles were screened by title and abstract for inclusion. A total of 21 papers reporting interventions integrating cervical cancer care and HIV services met the criteria for inclusion. All but one study described integration of cervical cancer screening services into existing HIV services**. Most programs also offered treatment of minor lesions, a 'screen-and-treat' approach, with some also offering treatment of larger lesions within the same visit. **Three distinct models of integration were identified**. One model described **integration within the same clinic through training of existing staff**. Another model described **integration through co-location of services**, with the third model describing **programs of integration through complex coordination across the care pathway**. **The studies suggested that integration of cervical cancer services with HIV services using all models was feasible and acceptable to patients. However, several barriers were reported, including high loss to follow up for further treatment, limited human-resources, and logistical and chain management support**. Using visual screening methods can facilitate screening and treatment of minor to larger lesions in a single 'screen-and-treat' visit. **Complex integration in a single-visit was shown to reduce loss to follow up.** The use of existing health infrastructure and funding together with comprehensive staff training and supervision, community engagement and digital technology were some of the many other facilitators for integration reported across models.

Conclusions: **This review shows that integration of cervical cancer screening and treatment with HIV services using different models of service delivery is feasible as well as acceptable to women living with HIV.** However, the descriptive nature of most papers and lack of data on the effect on long-term outcomes for HIV or cervical cancer limits the inference on the effectiveness of the integrated programs. There is a need for strengthening of health systems across the care continuum and for high quality studies evaluating the effect of integration on HIV as well as on cervical cancer outcomes.

Abstract Full-text [free] access

The burden of HIV on tuberculosis patients in the Volta region of Ghana from 2012 to 2015: implication for tuberculosis control.

Osei E, Der J, Owusu R, Kofie P, Axame WK. BMC Infect Dis. 2017 Jul 19;17(1):504. doi: 10.1186/s12879-017-2598-z.

Background: The impact of HIV on TB, and the implications for TB control, has been acknowledged as a public health challenge. It is imperative therefore to assess the burden of HIV on TB patients as an indicator for monitoring the control efforts of the two diseases in this part of the world. This study aimed at determining the burden of HIV infection in TB patients.

Methods: **We conducted a retrospective review of TB registers in five districts of the Volta Region of Ghana. Prevalence of TB/HIV co-infection was determined. Bivariate and multivariate logistic regression were used to identify the predictors of HIV infection among TB patients and statistical significance was set at p-value <0.05.**

Results: **Of the 1772 TB patients, 1633 (92.2%) were tested for HIV. The overall prevalence of TB/HIV co-infection was (18.2%**; 95% CI: 16.4-20.1). **The prevalence was significantly higher among females** (**24.1%**; 95%CI: 20.8-27.7), **compared to males** (**15.1%**; 95% CI: 13.1-17.4)

(p < 0.001) **and among children <15 years of age** (**27.0%**; 95% CI: 18.2-38.1**), compared to the elderly ≥70 years** (**3.5%**; 95% CI: 1.6-7.4) (p < 0.001). **Treatment success rate was higher among patients with only TB** (**90%**; 95% CI: 88.1-91.5) **than among TB/HIV co-infected patients** (**77.0%**; 95% CI: 71.7-81.7) (p < 0.001). **Independent predictors of HIV infection were found to be: being female** (AOR: 1.79; 95% CI: 1.38-2.13; p < 0.001); **smear negative pulmonary TB** (AOR: 1.84; 95% CI: 1.37-2.47; p < 0.001); **and patients registered in Hohoe, Kadjebi, and Kpando districts with adjusted odds ratios of 1.69** (95% CI: 1.13-2.54; p = 0.011), **2.29** (95% CI: 1.46-3.57; p < 0.001), **and 2.15** (95% CI: 1.44-3.21; p < 0.001) **respectively**. **Patients ≥70 years of age and those registered in Keta Municipal were less likely to be HIV positive with odds ratios of 0.09** (95% CI: 0.04-0.26; p < 0.001) **and 0.62** (95% CI: 0.38-0.99; p = 0.047) **respectively**.

Conclusion: **TB/HIV co-infection rate in five study districts of the Volta region is quite high, occurs more frequently in female patients than males; among smear negative pulmonary TB patients, and children <15 years of age. Findings also demonstrate that HIV co-infection affects TB treatment outcomes adversely**. Strengthening the TB/HIV collaborative efforts is required in order to reduce the burden of co-infection in patients.

Abstract Full-text [free] access

Cost-effectiveness of isoniazid preventive therapy among HIV-infected patients clinically screened for latent tuberculosis infection in Dar es Salaam, Tanzania: a prospective cohort study.

Shayo GA, Chitama D, Moshiro C, Aboud S, Bakari M, Mugusi F. BMC Public Health. 2017 Jul 19;18(1):35. doi: 10.1186/s12889-017-4597-9.

Background: One of the reasons why Isoniazid preventive therapy (IPT) for Tuberculosis (TB) is not widely used in low income countries is concerns on cost of excluding active TB. We analyzed the cost-effectiveness of IPT provision in Tanzania having ruled out active TB by a symptom-based screening tool.

Methods: **Data on IPT cost-effectiveness was prospectively collected from an observational cohort study of 1283 HIV-infected patients on IPT and 1281 controls; followed up for 24 months. The time horizon for the analysis was 2 years. Number of TB cases prevented and deaths averted were used for effectiveness. A micro costing approach was used from a provider perspective. Cost was estimated on the basis of clinical records, market price or interviews with medical staff**. We annualized the cost at a discount of 3%. A univariate sensitivity analysis was done. **Results are presented in US$ at an average annual exchange rate for the year 2012 which was Tanzania shillings 1562.4 for 1 US $.**

Results: **The number of TB cases prevented was 420/100 000 persons receiving IPT. The number of deaths averted was 979/100 000 persons receiving IPT. Incremental cost due to IPT provision was US$ 170 490. The incremental cost-effective ratio was US $ 405.93 per TB case prevented and US $ 174.15 per death averted. These costs were less than 3 times the 768 US $ Gross Domestic Product (GDP) per capita for Tanzania in the year 2014, making IPT provision after ruling out active TB by the symptom-based screening tool cost-effective**. The results were robust to changes in laboratory and radiological tests but not to changes in recurrent, personnel, medication and utility costs.

Conclusion: **IPT should be given to HIV-infected patients who screen negative to symptom-based TB screening questionnaire.** Its cost-effectiveness supports government policy to integrate

IPT to HIV/AIDS care and treatment in the country, given the availability of budget and the capacity of health facilities.

Abstract Full-text [free] access

Immunological recovery in tuberculosis/HIV co-infected patients on antiretroviral therapy: implication for tuberculosis preventive therapy.

Karo B, Krause G, Castell S, Kollan C, Hamouda O, Haas W; ClinSurv HIV Study Group. BMC Infect Dis. 2017 Jul 25;17(1):517. doi: 10.1186/s12879-017-2627-y.

Background: Understanding the immune response to combination antiretroviral therapy (cART) is essential for a clear approach to tuberculosis (TB) preventive therapy. **We investigated the immunological recovery in cART-treated HIV-infected patients developing TB compared to those who remained free of TB.**

Methods: **We extracted data of HIV-infected patients from a multicenter cohort for the HIV clinical surveillance in Germany**. **No patients included in our study had TB at the beginning of the observation. Using a longitudinal mixed model, we assessed the differences in the mean change of biomarkers (CD4+ cell count, CD8+ cell count, CD4:CD8 ratio and viral load) since cART initiation in patients who remained free of TB vs. those developing TB. To detect the best-fit trajectories of the immunological biomarkers, we applied a multivariable fractional polynomials model**.

Results: **We analyzed a total of 10 671 HIV-infected patients including 139 patients who developed TB during follow-up. The highest TB incidences were observed during the first two years since cART initiation (0.32 and 0.50 per 100 person-years).** In an adjusted multivariable mixed model, we found that the average change in CD4+ cell count recovery was significantly greater by 33 cells/μl in patients who remained free of TB compared with those developing TB. **After the initial three months of cART, 65.6% of patients who remaining free of TB achieved CD4+ count of ≥400 cells/μl, while only 11.3% of patients developing TB reached this immunological status after the three months of cART. We found no differences in the average change of CD8+ cell count, CD4:CD8 ratio or viral load between the two-patient groups.**

Conclusion: **All HIV-infected patients responded to cART. However, patients developing TB showed reduced recovery in CD4+ cell count and this might partly explain the incident TB in HIV-infected patients receiving cART.** These findings reinforce the importance of adjunctive TB preventive therapy for patients with reduced recovery in CD4+ cell count.

Abstract Full-text [free] access