Welcome to the 4th issue of HIV this month in 2017! In this issue, we cover the following topics:

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Peter Godfrey-Faussett and Celeste Sandoval
UNAIDS
1. HIV testing and treatment

HIV self-tests — these women loved them!

Editor’s notes: Encouraging HIV testing, particularly among hard to reach populations such as men, young people and people who do not regularly attend health services is one of the key challenges for the HIV response. Many countries have adopted the UNAIDS treatment target of 90:90:90, the goal of which is that 90% of all people living with HIV should know their status. WHO has recently released new guidance on the use of HIV self-tests as a screening test and on approaches to partner notification to encourage greater uptake of HIV testing. An interesting qualitative study by Maman S and colleagues explored in depth the attitudes and experiences of 18 female sex workers drawn from a larger ongoing study of HIV self-test approaches. These women described to the researchers how they had distributed up to five oral fluid based self-test kits to their partners, friends and clients. The results demonstrate the wide range of potential ways that such distribution might help not only with accessing HIV testing but also increasing dialogue about risk reduction. Two of the women did experience verbal or sexual abuse, but it is important to realize that women were selected from the larger parent study precisely because they had reported such abuse, in order to understand the context better. The women remained enthusiastic about distributing self-tests and felt that the benefits outweighed the risks in the challenging environment in which they work. Nonetheless, as the authors point out, the potential considerable benefits of scaling up HIV self-testing approaches need to be combined with ensuring that there is good communication about the risks, efforts to increase the agency of vulnerable women and support services for women experiencing intimate partner violence whether related to HIV testing or not.


Promoting awareness of serostatus and frequent HIV testing is especially important among high risk populations such as female sex workers (FSW) and their sexual partners. HIV self-testing is an approach that is gaining ground in sub-Saharan Africa as a strategy to increase knowledge of HIV status and promote safer sexual decisions. However, little is known about self-test distribution strategies that are optimal for increasing testing access among hard-to-reach and high risk individuals. We conducted a qualitative study with 18 FSW who participated in a larger study that provided them with five oral fluid-based self-tests, training on how to use the tests, and encouragement to offer the self-tests to their sexual partners using their discretion. Women demonstrated agency in the strategies they used to introduce self-tests to their partners and to avoid conflict with partners. They carefully considered with whom to share self-tests, often assessing the possibility for negative reactions from partners as part of their decision making process. When women faced negative reactions from partners, they drew on strategies they had used before to avoid conflict and physical harm from partners, such as not responding to angry partners and forgoing payment to leave angry partners quickly. Some women also used self-tests to make more informed sexual decisions with their partners.

Abstract  Full-text [free] access
Non-communicable diseases and co-morbidities – the flip side of successful ART programmes?

Editor’s notes: As the population of people living with HIV grows older and lives longer, the importance of non-communicable diseases is increasing. Several studies this month explored various aspects of this intersection.

An encouraging study from Spain by Sorigué M et al., analysed the outcomes of patients with advanced stage Hodgkin’s lymphoma, a relatively common cancer both among people living with HIV and the HIV-negative population. The authors showed that, in the era of combined antiretroviral therapy, the complete response rate and ten year survival were not significantly different among people living with HIV (89% and 73%) and HIV negative people (91% and 68%).

Another broadly encouraging study from Ireland by Tinago W et al., followed up 384 people (176 living with HIV) to determine changes over three years in their bone mineral density (BMD). BMD was somewhat lower in the people living with HIV, despite the group being younger on average. As expected, BMD gradually fell with increasing age but the rate of bone loss was no different between people living with HIV and HIV negative people. 88% of the people living with HIV were on ART at the start of the study period. Not having started ART among people living with HIV was associated with lower BMD and people who had started more recently showed the largest declines in BMD. This suggests (as has previously been shown in cohorts of people living with HIV) that after an initial loss in BMD, the rate of loss stabilizes and is similar to HIV-negative people. Interestingly, the authors did not show that overall exposure to tenofovir disoproxil fumarate (TDF) was particularly associated with greater BMD loss over the course of follow up, despite several previous randomized trials confirming that TDF does cause BMD loss when it is started.

While on the subject of TDF, this month saw two important regulatory trials of tenofovir alafenamide (TAF), sponsored by the manufacturers Gilead Sciences. 630 people living with HIV on treatment with rilpivirine, emtricitabine and TDF whose viral load was supressed, were randomly allocated to remain on the same regimen or to swap the TDF for TAF. TAF is a pro-drug, that reduces the plasma concentrations of tenofovir and is therefore expected to reduce the renal and bone toxicities associated with TDF while still delivering active drug to the cells where it is needed. One year later, viral suppression was very similar in the two groups (94%). There was also no significant difference seen in the side effects over this one year period, with no serious adverse events and 6% vs. 12% having some side effects in the TAF and TDF arms respectively [Orkin C and colleagues].

A related study by DeJesus E et al. with the same design was conducted among people taking efavirenz, emtricitabine and tenofovir, one of the most common first line regimens throughout the world. In this trial the efavirenz was switched to rilpivirine and the TDF to TAF. 875 people living with HIV whose viral load was supressed were randomized and after one year viral suppression was very similar in the two groups (90-92%). There was also no significant difference seen in the side effects over this one year period, with no serious adverse events and 13% vs. 10% having some side effects in the rilpivirine - TAF and efavirenz - TDF arms respectively.

Returning to co-morbidities and non-communicable diseases, a study by Rodríguez-Arboli E and colleagues in rural Tanzania has shown that 11.6% of people living with HIV who had not yet started ART had raised blood pressure. A further 9.6% develop raised blood pressure during follow up, an incidence of 12 per 100 person years. The risk factors for developing hypertension were those well recognized in HIV-negative populations (age, renal disease and being overweight) and not specifically related to HIV infection, ART or immunological status. The authors recommend integration of non-communicable disease screening and management into HIV care clinics but a larger conclusion might
be to improve management of hypertension more generally, as it affects both people living with HIV and people without.

In contrast, a study by Pollack TM et al. from Viet Nam shows that smoking tobacco is associated with a higher viral load among people living with HIV presenting for ART. As would be expected, other predictors of more advanced HIV disease such as lower CD4 counts and lower BMI and prior TB were all associated with a higher viral load at presentation. Male sex was also significantly associated with a higher viral load. The authors point out various other studies from Cameroon and the US that have shown similar and related interactions between smoking tobacco, viral load at presentation or viral load suppression or rebound on ART treatment. Other studies in the US have not found this association. One of the challenges is to separate behavioural factors that might be confounders – perhaps people who smoke are more likely to present late. In this study there was not a clear dose response. People who smoked more than ten cigarettes per day were actually somewhat less likely in this sample to have a higher viral load than people who smoked 1-10 cigarettes per day, but the numbers were too small to make statistically significant claims. The authors suggest that oxidative stress and induction of the cytochrome P450 (CYP) pathway could explain the mechanism of smoking-related increased VL among HIV positive individuals. While the study cannot prove cause and effect, there are already many reasons to promote tobacco cessation among people living with HIV and this may be an additional one.

The D:A:D study is a major prospective cohort that follows more than 49 000 people living with HIV in Europe, Australia and the USA. Among the cohort, more than 4000 have developed chronic renal impairment. A study by Ryom L et al. this month examined whether there was improvement, stabilisation or progression of renal impairment in the 2006 individuals who had additional measurements 2-3 years after renal impairment was first noted and explored risk factors for each. On the one hand, they show that some ARVs (notably TDF and ritonavir-boosted atazanovir) are associated with worse renal outcomes, but on the other hand, they demonstrate that after stopping these nephrotoxic medicines, the kidneys recover or at least do not deteriorate further. Once again, traditional risk factors (older age, high blood pressure and diabetes) are also important risk factors for the kidneys of people living with HIV. As the population of people living with HIV gets older and lives longer, HIV care and traditional non-communicable disease management must overlap and coordinate.

HIV-infection has no prognostic impact on advanced-stage Hodgkin lymphoma treated with doxorubicin, bleomycin, vinblastine and dacarbazine.


Objective: Classical Hodgkin lymphoma (cHL) is a non-AIDS-defining cancer with good response to chemotherapy in the combined antiretroviral therapy (cART) era. The aim of the study was to compare the characteristics, the response with treatment and survival of advanced-stage cHL treated with adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) between cART-treated HIV-positive and HIV-negative patients.

Design and methods: We retrospectively analyzed advanced-stage cHL patients from a single institution, uniformly treated with ABVD. All HIV-positive patients received cART concomitantly with ABVD.

Results: A total of 69 patients were included in the study: 21 were HIV-positive and 48 were HIV-negative. HIV-positive patients had more aggressive features at cHL diagnosis, such as worse
performance status, more frequent bone marrow involvement and mixed cellularity histologic subtype.

There were no differences in complete response rate (89% in HIV-positive vs. 91% in HIV-negative), P=1; disease-free survival 10-year disease-free survival 70% (41-99%) vs. 74% (57-91%), P=0.907 and overall survival (OS) 10-year OS 73% (95% confidence interval 52-94%) vs. 68% (51-85%), P=0.904. On multivariate analysis, HIV infection did not correlate with worse OS.

Conclusion: Although HIV-positive patients with cHL had more aggressive baseline features in this series, there were no differences in response rate or survival between HIV-positive and HIV-negative patients.

Abstract access

Predictors of longitudinal change in bone mineral density in a cohort of HIV-positive and negative patients.


Objective: Although low bone mineral density (BMD) is prevalent in HIV, changes in BMD over time remain unclear. We aimed to compare rates of, and factors associated with, BMD change between HIV-positive and HIV-negative patients.

Methods: In a prospective, 3-year cohort, HIV-positive and HIV-negative patients provided annual demographic and clinical data, fasting bloods, and dual x-ray absorptiometry. Using longitudinal mixed models we compared and determined predictors of rate of change in BMD.

Results: Of 384 study participants (45.8% HIV positive), 120 contributed two and 264 contributed three BMD measurements. Those with HIV were younger [median interquartile range 39 (34-46) vs. 43 (35-50) years; P=0.04], more often men (61 vs. 46%; P=0.003), and less likely Caucasian (61 vs. 82%; P<0.001). Although BMD was lower in those with HIV, BMD declined in both groups, with nonsignificant between-group difference in rate of BMD change over time. Within the HIV group, starting antiretroviral therapy (ART) within 3 months of enrolment was associated with greater BMD decline at all anatomical sites (all P<0.001). Age more than 30 years, Caucasian ethnicity, and not being on ART during follow-up were associated with greater decline and higher parathyroid hormone associated with a smaller decline in BMD at the femoral neck. We found no association between BMD change and exposure to tenofovir disoproxil fumarate or protease inhibitors.

Conclusion: We observed no difference in rate of BMD decline regardless of HIV status and in HIV-positive patient, having started ART within the previous 3 months was the only factor associated with greater BMD decline at all three sites.

Abstract access

Switching from tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study.

Background: Tenofovir alafenamide, a tenofovir prodrug, results in 90% lower tenofovir plasma concentrations than does tenofovir disoproxil fumarate, thereby minimising bone and renal risks. We investigated the efficacy, safety, and tolerability of switching to a single-tablet regimen containing rilpivirine, emtricitabine, and tenofovir alafenamide compared with remaining on rilpivirine, emtricitabine, and tenofovir disoproxil fumarate.

Methods: In this randomised, double-blind, multicentre, placebo-controlled, non-inferiority trial, HIV-1-infected adults were screened and enrolled at 119 hospitals in 11 countries in North America and Europe. Participants were virally suppressed (HIV-1 RNA <50 copies per ml) on rilpivirine, emtricitabine, and tenofovir disoproxil fumarate for at least 6 months before enrolment and had creatinine clearance of at least 50 ml/min. Participants were randomly assigned (1:1) to receive a single-tablet regimen of either rilpivirine (25 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) or to remain on a single-tablet regimen of rilpivirine (25 mg), emtricitabine (200 mg), and tenofovir disoproxil fumarate (300 mg), with matching placebo, once daily for 96 weeks. Investigators, participants, study staff, and those assessing outcomes were masked to treatment group. All participants who received one dose of study drug and were on the tenofovir disoproxil fumarate regimen before screening were included in primary efficacy analyses. The primary endpoint was the proportion of participants with less than 50 copies per ml HIV-1 RNA at week 48 (by the US Food and Drug Administration snapshot algorithm), with a prespecified non-inferiority margin of 8%. This study was registered with clinicaltrials.gov, number NCT01815736.

Findings: Between Jan 26, 2015, and Aug 25, 2015, 630 participants were randomised (316 to the tenofovir alafenamide group and 314 to the tenofovir disoproxil fumarate group). At week 48, 296 (94%) of 316 participants on tenofovir alafenamide and 294 (94%) of 313 on tenofovir disoproxil fumarate had maintained less than 50 copies per ml HIV-1 RNA (difference -0.3%, 95.001% CI -4.2 to 3.7), showing non-inferiority of tenofovir alafenamide to tenofovir disoproxil fumarate. Numbers of adverse events were similar between groups. 20 (6%) of 316 participants had study-drug related adverse events in the tenofovir alafenamide group compared with 37 (12%) of 314 in the tenofovir disoproxil fumarate group; none of these were serious.

Interpretation: Switching to rilpivirine, emtricitabine, and tenofovir alafenamide was non-inferior to continuing rilpivirine, emtricitabine, tenofovir disoproxil fumarate in maintaining viral suppression and was well tolerated at 48 weeks. These findings support guidelines recommending tenofovir alafenamide-based regimens, including coformulation with rilpivirine and emtricitabine, as initial and ongoing treatment for HIV-1 infection.

Abstract access

Switching from efavirenz, emtricitabine, and tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study.


Background: Tenofovir alafenamide is a prodrug that reduces tenofovir plasma concentrations by 90% compared with tenofovir disoproxil fumarate, thereby decreasing bone and renal risks. The coformulation of rilpivirine, emtricitabine, and tenofovir alafenamide has recently been approved,
and we aimed to investigate the efficacy, safety, and tolerability of switching to this regimen compared with remaining on coformulated efavirenz, emtricitabine, and tenofovir disoproxil fumarate.

Methods: In this randomised, double-blind, placebo-controlled, non-inferiority trial, HIV-1-infected adults were enrolled at 120 hospitals and outpatient clinics in eight countries in North America and Europe. Participants were virally suppressed (HIV-1 RNA <50 copies per mL) on efavirenz, emtricitabine, and tenofovir disoproxil fumarate for at least 6 months before enrolment and had creatinine clearance of at least 50 mL/min. Participants were randomly assigned (1:1) to receive a single-tablet regimen of rilpivirine (25 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) or to continue a single-tablet regimen of efavirenz (600 mg), emtricitabine (200 mg), and tenofovir disoproxil fumarate (300 mg), with matching placebo. Investigators, participants, study staff, and those assessing outcomes were masked to treatment group. The primary endpoint was the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 (assessed by the US Food and Drug Administration snapshot algorithm), with a prespecified non-inferiority margin of 8%. This study was registered with ClinicalTrials.gov, number NCT02345226.

Findings: Between Jan 26, 2015, and Aug 27, 2015, 875 participants were randomly assigned and treated (438 with rilpivirine, emtricitabine, and tenofovir alafenamide and 437 with efavirenz, emtricitabine, tenofovir disoproxil fumarate). Viral suppression at week 48 was maintained in 394 (90%) of 438 participants assigned to the tenofovir alafenamide regimen and 402 (92%) of 437 assigned to the tenofovir disoproxil fumarate regimen (difference -2.0%, 95.001% CI -5.9 to 1.8), demonstrating non-inferiority. 56 (13%) of 438 in participants in the rilpivirine, emtricitabine, and tenofovir alafenamide group experienced treatment-related adverse events compared with 45 (10%) of 437 in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group.

Interpretation: Switching to rilpivirine, emtricitabine, and tenofovir alafenamide from efavirenz, emtricitabine, and tenofovir disoproxil fumarate was non-inferior in maintaining viral suppression and was well tolerated at 48 weeks. These findings support guidelines recommending tenofovir alafenamide-based regimens, including coformulation with rilpivirine and emtricitabine, as initial and ongoing treatment for HIV-1 infection.

Abstract access

Incidence and risk factors for hypertension among HIV patients in rural Tanzania - A prospective cohort study.


Introduction: Scarce data are available on the epidemiology of hypertension among HIV patients in rural sub-Saharan Africa. We explored the prevalence, incidence and risk factors for incident hypertension among patients who were enrolled in a rural HIV cohort in Tanzania.

Methods: Prospective longitudinal study including HIV patients enrolled in the Kilombero and Ulanga Antiretroviral Cohort between 2013 and 2015. Non-ART naïve subjects at baseline and pregnant women during follow-up were excluded from the analysis. Incident hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on two consecutive visits. Cox proportional hazards models were used to assess the association of baseline characteristics and incident hypertension.
Results: Among 955 ART-naïve, eligible subjects, 111 (11.6%) were hypertensive at recruitment. Ten women were excluded due to pregnancy. The remaining 834 individuals contributed 7967 person-months to follow-up (median 231 days, IQR 119-421) and 80 (9.6%) of them developed hypertension during a median follow-up of 144 days from time of enrolment into the cohort [incidence rate 120.0 cases/1000 person-years, 95% confidence interval (CI) 97.2-150.0]. ART was started in 630 (75.5%) patients, with a median follow-up on ART of 7 months (IQR 4-14). Cox regression models identified age [adjusted hazard ratio (aHR) 1.34 per 10 years increase, 95% CI 1.07-1.68, p = 0.010], body mass index (aHR per 5 kg/m² 1.45, 95% CI 1.07-1.99, p = 0.018) and estimated glomerular filtration rate (aHR < 60 versus ≥ 60 ml/min/1.73 m² 3.79, 95% CI 1.60-8.99, p = 0.003) as independent risk factors for hypertension development.

Conclusions: The prevalence and incidence of hypertension were high in our cohort. Traditional cardiovascular risk factors predicted incident hypertension, but no association was observed with immunological or ART status. These data support the implementation of routine hypertension screening and integrated management into HIV programmes in rural sub-Saharan Africa.

Abstract  Full-text [free] access

Cigarette smoking is associated with high HIV viral load among adults presenting for antiretroviral therapy in Vietnam.


High HIV viral load (VL >100 000 cp/ml) is associated with increased HIV transmission risk, faster progression to AIDS, and reduced response to some antiretroviral regimens. To better understand factors associated with high VL, we examined characteristics of patients presenting for treatment in Hanoi, Vietnam. We examined baseline data from the Viral Load Monitoring in Vietnam Study, a randomized controlled trial of routine VL monitoring in a population starting antiretroviral therapy (ART) at a clinic in Hanoi. Patients with prior treatment failure or ART resistance were excluded. Characteristics examined included demographics, clinical and laboratory data, and substance use. Logistic regression was used to calculate crude and adjusted odds ratios (aOR) and 95% confidence intervals (95% CI). Out of 636 patients, 62.7% were male, 72.9% were ≥30 years old, and 28.3% had a history of drug injection. Median CD4 was 132cells/mm³, and 34.9% were clinical stage IV. Active cigarette smoking was reported by 36.3% with 14.0% smoking >10 cigarettes per day. Alcohol consumption was reported by 20.1% with 6.1% having ≥5 drinks per event. Overall 53.0% had a VL >100 000 cp/ml. Male gender, low body weight, low CD4 count, prior TB, and cigarette smoking were associated with high VL. Those who smoked 1-10 cigarettes per day were more likely to have high VL (aOR = 1.99, 95% CI = 1.15-3.45), while the smaller number of patients who smoked >10 cigarettes per day had a non-significant trend toward higher VL (aOR = 1.41, 95% CI = 0.75-2.66). Alcohol consumption was not significantly associated with high VL. Tobacco use is increasingly recognized as a contributor to premature morbidity and mortality among HIV-infected patients. In our study, cigarette smoking in the last 30 days was associated with a 1.5 to 2-fold higher odds of having an HIV VL >100 000 cp/ml among patients presenting for ART. These findings provide further evidence of the negative effects of tobacco use among HIV-infected patients.

Abstract  Full-text [free] access
Predictors of eGFR progression, stabilisation or improvement after chronic renal impairment in HIV-positive individuals.


Objectives: The objectives of this analysis were to investigate predictors of progression, stabilisation or improvement in eGFR after development of chronic renal impairment (CRI) in HIV-positive individuals.

Design: Prospective observational study.

Methods: D:A:D study participants progressing to CRI defined as confirmed, ≥ 3 months apart, eGFR ≤ 70 mL/min/1.73m were included in the analysis. The median of all eGFRs measured 24-36 months post-CRI was compared to the median eGFR defining CRI, and changes were grouped into: improvement (> +10 mL/min/1.73m), stabilisation (-10 to +10 mL/min/1.73m) and progression (< -10 mL/min/1.73m). Adjusted polynomial regression models assessed odds of better eGFR outcomes after CRI, assuming eGFR improvement is better than stabilisation which in turn is better than progression.

Results: Of 2006 individuals developing CRI, 21% subsequently improved eGFR, 67% stabilised and 12% progressed. Individuals remaining on TDF or boosted atazanavir (ATV/r) 24 months post-CRI had worse eGFR outcomes compared to those unexposed (TDF: 0.47 [0.35-0.63], ATV/r: 0.63 [0.48-0.82]). Individuals off TDF for 12-24 months (0.75 [0.50-1.13]) or off ATV/r for >12 months (1.17 [0.87-1.57]) had similar eGFR outcomes as those unexposed to these ARVs. Older age, hypertension, later date of CRI and diabetes were associated with worse eGFR outcomes.

Conclusion: Current TDF and ATV/r use after a diagnosis of CRI was associated with worse eGFR outcomes. In contrast, TDF and ATV/r discontinuation lead to similar longer-term eGFR outcomes as in those unexposed suggesting these drug-associated eGFR declines may be halted or reversed after their cessation.

Abstract access

**HIV-2 – not a global pandemic, but still causing challenges for diagnosis and treatment**

*Editor’s notes:* HIV-2 is discussed much less than HIV-1 because it has not caused a global pandemic. Nonetheless there are around 1-2 million people thought to be living with HIV-2, predominantly in West Africa and in Portugal and her historical connections (Brazil, Angola, Mozambique and India). A useful review by de Mendoza C and colleagues from Spain highlights key features in the epidemiology, management and future directions for HIV-2. The diagnosis is easy to miss and should be considered whenever routine HIV-1 tests give curious serological profiles. There are also important differences when treating people living with HIV-2. HIV-2 cannot be treated with non-nucleoside reverse transcriptase inhibitors and some protease inhibitors do not work either. Viral load monitoring has not been commercialized, and so is often unreliable. CD4 cell counts tend to drop more rapidly in HIV-1 and this has sometimes led to the suggestion that HIV-2 is a benign infection. However, progression to an AIDS-like syndrome does occur, particularly in people who acquired HIV at a younger age. The CD4 cell count recovery on antiretroviral therapy seem to be less effective in HIV-2 compared to HIV-1 infections. Failure and selection of drug resistance may be more frequent in HIV-2.
HIV-2 Epidemic in Spain - challenges and missing opportunities.


HIV type 2 (HIV-2) is a neglected virus despite estimates of 1-2 million people infected worldwide. HIV-2 is less efficiently transmitted than HIV-1 by sex and from mother-to-child. Although AIDS may develop in HIV-2 carriers, it takes longer than in HIV-1-infected patients. In contrast with HIV-1 infection, there is no global pandemic caused by HIV-2, remaining the virus largely confined to West Africa. In a less extent and due to socioeconomic ties and wars, HIV-2 is prevalent in Portugal and its former colonies in Brazil, India, Mozambique and Angola. Globally, HIV-2 infections are steadily declining over time. A total of 338 cases of HIV-2 infection had been reported at the Spanish HIV-2 registry until December 2016, of whom 63% were male. Overall 72% were sub-Saharan Africans whereas 16% were native Spaniards. Dual HIV-1 and HIV-2 coinfection was found in 9% of patients. Heterosexual contact was the most likely route of HIV-2 acquisition in more than 90% of cases. Roughly one third presented with CD4 counts <200 cells/μL and/or AIDS clinical events. Plasma HIV-2 RNA was undetectable at baseline in 40% of patients. To date, one third of HIV-2 carriers have received antiretroviral therapy, using integrase inhibitors 32 individuals. New diagnoses of HIV-2 in Spain have remained stable since 2010 with an average of 15 cases yearly. Illegal immigration from Northwestern African borders accounts for over 75% of new HIV-2 diagnoses. Given the relatively large community of West Africans already living in Spain and the continuous flux of immigration from endemic regions, HIV-2 infection either alone or as coinfection with HIV-1 should be excluded once in all HIV-seroreactive persons, especially when showing atypical HIV serological profiles, immunovirological disconnect (CD4 count loss despite undetectable HIV-1 viremia) and/or high epidemiological risks (birth in or sex partners from endemic regions).

Abstract access

2. Combination prevention

Phylogenetics - powerful new tools tied to ethical imperatives for key populations

Editor's notes: There are now well over half a million HIV isolates that have been sequenced and the data stored in public accessible Genbank. A systematic review by Hassan AS and colleagues of the methods used to define phylogenetic trees and clusters within them demonstrates the importance of using the correct criteria for the hypothesis being tested. Most articles use the pol sequence, since this is what is sequenced for drug resistance testing. Most analyses have been done using a phylogenetic approach that uses a probability to assess the likelihood that isolates are clustered, and so depends on the cut-off value chosen. For example, a well-studied outbreak of HIV among drug users in Finland is clearly linked to an earlier outbreak in Sweden, but because the Finnish isolates were collected later, they had already diverged somewhat from the Swedish ones. If the threshold was set too high, they would not be recognized to be part of the same outbreak. However for active transmission chains, a high threshold is needed to avoid falsely linking isolates. There is no consensus on what methods to use, so caution is needed when comparing different studies.

Mark Wainberg, Professor of Medicine and of Microbiology at McGill University and a giant of Canadian HIV science, passed away this month. So, as a tribute to his work, we have chosen a study from the McGill AIDS Centre by Brenner BG and colleagues. The team used phylogenetic analysis to classify pre-treatment HIV isolates from 3901 men who have sex with men in Quebec according to the
likelihood of being an acute or recent infection and the likelihood of clustering with other isolates. Over the period from 2002-2015, a larger and larger proportion of the infections in this population could be linked to larger clusters, particularly involving younger men and men with recent infection, many of whom did not know their HIV status. At least 40% of the onward spread of the epidemic in Quebec can be ascribed to just thirty clusters, varying in size from 20–140 individuals.

Using phylogenetics to understand transmission patterns requires careful attention to ethics, confidentiality and stigmatization. A study in South Korea by Ahn MY and colleagues aimed to define the risk factors for clustering within clusters among 143 people living with HIV in four cities. In eight out of the nine clusters identified participants did not report the same risk factors. Clusters were small, eight pairs and one quartet. In the two tightest clusters, where the isolates were indistinguishable on the sequences examined, one man stated that he had sex with women, but the paired isolate came from another man and in the other pair, both men chose not to disclose their risk factors. With small studies where information can sometimes be inferred even when not disclosed, it is perhaps not surprising that more than half the participants chose not to report their risk factors.

Other phylogenetic studies this month have explored the evolution of HIV recombinase and the spread of different clades in communities in North-Eastern Brazil [Delatorre E et al.] and China. In the North-Eastern states of Brazil, 72% of HIV isolates were subtype B, but rare subtypes such as D (1%) and CRF02_AG (1%) appear to be spreading within the population rather than being introduced from outside. In China studies from Sichuan [Wang Y et al.], Yunnan [Li Y and colleagues] and Zhejiang [Wang H et al.] have shown new recombinant forms of HIV with elements that suggest that viruses from different countries in the region have combined. The widening diversity of HIV brings challenges for vaccine development, and potentially for HIV assays, such as those for recent infection that may differ in their sensitivity and specificity between different sub-types. Understanding the migration of people and their viruses could be useful for providing better services, but careful attention to messaging will be needed to prevent such data from being used to discriminate further against migrants.

The final phylogenetic paper this month also comes from China, where Hao M and colleagues reported a study of students living with HIV in Beijing. The study demonstrated that transmitted drug resistance is still low in this setting, with just 0.8% of 237 students having virus that was resistant to non-nucleoside reverse transcriptase inhibitors that form part of the backbone of first line treatment in China. A further 1.3% has resistance to protease inhibitors that are used in second line treatment.

Defining HIV-1 transmission clusters based on sequence data: a systematic review and perspectives.


Understanding HIV-1 transmission dynamics is relevant to both screening and intervention strategies of HIV-1 infection. Commonly, HIV-1 transmission chains are determined based on sequence similarity assessed either directly from a sequence alignment or by inferring a phylogenetic tree. This review is aimed at both nonexperts interested in understanding and interpreting studies of HIV-1 transmission, and experts interested in finding the most appropriate cluster definition for a specific dataset and research question. We start by introducing the concepts and methodologies of how HIV-1 transmission clusters usually have been defined. We then present the results of a systematic review of 105 HIV-1 molecular epidemiology studies summarizing the most popular methods and definitions in the literature. Finally, we offer our perspectives on how HIV-1
transmission clusters can be defined and provide some guidance based on examples from real life datasets.

Abstract access

Large cluster outbreaks sustain the HIV epidemic among MSM in Quebec.


Objective: HIV-1 epidemics among MSM remain unchecked despite advances in treatment and prevention paradigms. This study combined viral phylogenetic and behavioural risk data to better understand underlying factors governing the temporal growth of the HIV epidemic among MSM in Quebec (2002-2015).

Methods: Phylogenetic analysis of pol sequences was used to deduce HIV-1transmission dynamics (cluster size, size distribution and growth rate) in first genotypes of treatment-naïve MSM (2002-2015, n=3901). Low sequence diversity of first genotypes (0-0.44% mixed base calls) was used as an indication of early-stage infection. Behavioural risk data were obtained from the Montreal rapid testing site and primary HIV-1-infection cohorts.

Results: Phylogenetic analyses uncovered high proportion of clustering of new MSM infections. Overall, 27, 45, 53 and 57% of first genotypes within one (singleton, n=1359), 2-4 (n=692), 5-9 (n=367), 10-19 (n=405) and 20+ (n=1277) cluster size groups were early infections (<0.44% diversity). Thirty viruses within large 20+ clusters disproportionately fuelled the epidemic, representing 13, 25 and 42% of infections, first genotyped in 2004-2007 (n=1314), 2008-2011 (n=1356) and 2012-2015 (n=1033), respectively. Of note, 35, 21 and 14% of MSM belonging to 20+, 2-19 and one (singleton) cluster groups were under 30 years of age, respectively. Half of persons seen at the rapid testing site (2009-2011, n=1781) were untested in the prior year. Poor testing propensity was associated with fewer reported partnerships.

Conclusion: Addressing the heterogeneity in transmission dynamics among HIV-1-infected MSM populations may help guide testing, treatment and prevention strategies.

Abstract access

HIV-1 transmission networks across South Korea.


Molecular epidemiology can help clarify the properties and dynamics of HIV-1 transmission networks in both global and regional scales. We studied 143 HIV-1-infected individuals recruited from four medical centers of three cities in South Korea between April 2013 and May 2014. HIV-1 env V3 sequence data were generated (337-793 bp) and analyzed using a pairwise distance-based clustering approach to infer putative transmission networks. Participants whose viruses were ≤2.0% divergent according to Tamura-Nei 93 genetic distance were defined as clustering. We collected demographic, risk, and clinical data and analyzed these data in relation to clustering. Among 143 participants, we identified nine putative transmission clusters of different sizes (range 2-4 participants). The reported risk factor of participants were concordant in only one network involving two
Participants, that is, both individuals reported homosexual sex as their risk factor. The participants in the other eight networks did not report concordant risk factors, although they were phylogenetically linked. About half of the participants refused to report their risk factor. Overall, molecular epidemiology provides more information to understand local transmission networks and the risks associated with these networks.

Abstract access

HIV-1 Genetic diversity in northeastern Brazil: high prevalence of non-B subtypes.


The Northeastern Brazilian region has experienced a constant increase in the number of newly reported AIDS cases over the last decade, but the genetic diversity of HIV-1 strains currently disseminated in this region remains poorly explored. HIV-1 pol sequences were obtained from 140 patients followed at outpatient clinics from four Northeastern Brazilian states (Alagoas, Bahia, Ceará and Piauí) between 2014 and 2015. Subtype B was the most prevalent HIV-1 clade (72%) detected in the Northeastern region, followed by subtypes F1 (6%), C (5%) and D (1%). The remaining strains (16%) displayed a recombinant structure and were classified as: BF1 (11%), BC (4%), BCF1 (1%) and CRF02_AG-like (1%). The 20 HIV-1 BF1 and BC recombinant sequences detected were distributed among 11 lineages classified as: CRF28/29_BF-like (n = 5), CRF39_BF-like (n = 1), URFs_BF (n = 9) and URFs_BC (n = 5). Non-B subtypes were detected in all Northeastern Brazilian states, but with variable prevalence, ranging from 16% in Ceará to 55% in Alagoas. Phylogenetics analyses support that subtype D and CRF02_AG strains detected in the Northeastern region resulted from the expansion of autochthonous transmission networks, rather than from exogenous introductions from other countries. These results reveal that HIV-1 epidemic spreading in the Northeastern Brazilian region is comprised by multiple subtypes and recombinant strains and that the molecular epidemiologic pattern in this Brazilian region is much more complex than originally estimated.

Abstract access

Identification of a novel HIV type 1 CRF01_AE/B'/C recombinant isolate in Sichuan, China.


We report in this study a novel HIV-1 unique recombinant virus (XC2014EU01) isolated from an HIV-positive man who infected through heterosexual sex in Sichuan, China. The near full-length genome analyses showed that XC2014EU01 harbored one subtype B segment in pol region and two subtype C segments in gag-pol region in a CRF01_AE backbone. The unique mosaic structure was distinctly different from the other CRF01_AE/B'/C recombinant forms reported. Phylogenetic tree analyses revealed that the subtype B region originated from a Thailand subtype B' lineage, the subtype C regions were from an India C lineage, and the backbone was from CRF01_AE. XC2014EU01 was still identified as CCR5-tropic, and plasma of XC2014EU01 infected person had the media neutralizing activity. The emergence of XC2014EU01 may increase the complexity of the HIV-1 epidemic among high-risk populations and the difficulty of vaccine research and development.
Identification of a novel HIV type 1 circulating recombinant form (CRF86_BC) among heterosexuals in Yunnan, China.


In recent years, multiple circulating recombinant forms (CRFs) and unique recombinant forms of human immunodeficiency virus type 1 (HIV-1) have been described in Yunnan, China. Here, we identified a novel HIV-1 CRF (CRF86_BC) isolated from three heterosexuals with no obvious epidemiologic linkage in western Yunnan (Baoshan prefecture) in China. CRF86_BC had a subtype C backbone with four subtype B fragments inserted into the pol, vpr, vpu, env, and nef gene regions, respectively. Furthermore, subregion tree analysis revealed that subtype C backbone originated from an Indian C lineage and subtype B segment inserted was from a Thai B lineage. They are different from previously documented B/C forms in its distinct backbone, inserted fragment size, and break points. This highlighted the importance of continual monitoring of genetic diversity and complexity of HIV-1 strains in this region.

Near full-length genomic characterization of a novel HIV-1 unique recombinant (CRF55_01B/CRF07_BC) from a Malaysian immigrant worker in Zhejiang, China.


Recombinant forms contribute substantially to the genetic diversity of human immunodeficiency virus type 1 (HIV-1). Here we report a novel HIV-1 recombinant detected from a comprehensive HIV-1 molecular epidemiologic study among cross-border populations in China. Near full-length genome (NFLG) phylogenetic analysis showed that the novel HIV-1 recombinant ZJCIQ15005, which was isolated from a Malaysian immigrant worker in Zhejiang, China, clustered with CRF55_01B reference sequences but set up a distinct branch. Recombinant analysis showed that the NFLG of ZJCIQ15005 composed of CRF55_01B (as the backbone) and CRF07_BC, with 12 recombinant break points observed in the pol, vif, vpr, tat, rev, env, nef, and 3’LTR regions. This is the first detection of a novel HIV-1 recombinant (CRF55_01B/CRF07_BC) in immigrant workers in China. The emergence of this recombinant may increase the complexity of the HIV-1 epidemic in China and suggests the importance of continuous surveillance of the dynamic changes of HIV-1.

Low rates of transmitted drug resistances among treatment-naive HIV-1 infected students in Beijing, China.


Beijing has seen a rising epidemic of HIV among students. However, little information was known about the molecular epidemiologic data among HIV-infected students. In this study, the diversity and the prevalence of TDR in pol sequences deriving from 237 HIV-infected students were analyzed. TDR mutations were found in 5 MSM among students. The overall prevalence of TDR
in students was 2.1%, comprised of 1.3% to protease inhibitors and 0.8% to non-nucleoside reverse transcriptase inhibitors. Our finding indicates a low-level prevalence of TDR mutations among students in Beijing.

Abstract access

Post-exposure prophylaxis – does it matter which medicines we use?

Editor’s notes: Two studies this month looked at alternative post-exposure prophylaxis (PEP) regimens. PEP is often not well tolerated and this leads to non-completion of the one month course. In London a randomized trial by Milinkovic A and colleagues compared the tolerability and completion rates between 213 individuals given twice daily maraviroc or ritonavir-boosted lopinavir in addition to daily tenofovir disoproxil fumarate with emtricitabine (TDF-FTC) daily. Completion rates were very similar (71% vs. 65%) but maraviroc was associated with fewer mild-moderate side effects (70% vs. 91%) and less use of anti-diarrhoeal medication (25% vs. 67%). There were no serious side effects in either arm and similar numbers of individuals stopped taking their medication (18%). In Australia, in an open label, non-randomized study, 100 individuals were offered once daily dolutegravir as the third drug (also with TDF-FTC). 90 people completed the one month course, 9 were lost to follow up and one stopped because of headaches. Side effects were also common in this study (similar to the London study): around a quarter of people complained of fatigue, nausea or diarrhoea [Mcallister J et al.]. Although no seroconversions were seen in either study, despite well documented risks at entry to treatment, the studies are not large enough to shed much light on the effectiveness of the regimens. They demonstrate the ongoing challenges in finding PEP regimens that have fewer side effects. Whether completion rates would be as high in less controlled settings than a clinical trial is not clear. Nonetheless it seems that dolutegravir daily or maraviroc twice daily may be a suitable replacement for ritonavir-boosted lopinavir as the third drug for use as PEP.

Randomized controlled trial of the tolerability and completion of maraviroc compared with Kaletra® in combination with Truvada® for HIV post-exposure prophylaxis (MiPEP Trial).


Objectives: Post-exposure prophylaxis (PEP) for HIV is often poorly tolerated and not completed. Alternative PEP regimens may improve adherence and completion, aiding HIV prevention. We conducted a randomized controlled trial of a maraviroc-based PEP regimen compared with a standard-of-care regimen using ritonavir-boosted lopinavir.

Methods: Patients meeting criteria for PEP were randomized to tenofovir disoproxil/emtricitabine (200/245 mg) once daily plus ritonavir-boosted lopinavir (Kaletra® 400/100 mg) or maraviroc 300 mg twice daily. The composite primary endpoint was completion of 28 days of the allocated PEP regimen without grade 3 or 4 clinical or laboratory adverse events (AEs) related to the PEP medication.

Results: Two hundred and thirteen individuals were randomized (107 to maraviroc; 106 to Kaletra® arm). Follow-up rates were high in both groups. There was no difference in the primary endpoint: 70 (71%) in the maraviroc and 64 (65%) in the Kaletra® arm ($P = 0.36$) completed PEP without grade 3 or 4 AEs. Discontinuation of PEP was the same (18%) in both groups. There were no grade 3 or 4 clinical AEs in either arm, but more grade 1 or 2 clinical AEs in the Kaletra®
arm (91% versus 70%; P < 0.001). Antidiarrhoeal medication use was higher in the Kaletra® arm (67% versus 25%; P < 0.001). There were no HIV seroconversions in the study period.

Conclusions: The completion rate in the absence of grade 3 or 4 AEs was similar with both regimens. Maraviroc-based PEP was better tolerated, supporting its use as an option for non-occupational PEP.

Abstract access

Dolutegravir with tenofovir disoproxil fumarate - emtricitabine as HIV post-exposure prophylaxis in gay and bisexual men.


Objectives: Completion rates for HIV post-exposure prophylaxis (PEP) are often low. We investigated the adherence and safety of dolutegravir (DTG 50mg daily) with tenofovir disoproxil fumarate 300mg/emtricitabine 200mg (TDF-FTC) as 3-drug PEP in gay and bisexual men (GBM).

Design: Open-label, single-arm study at 3 sexual health clinics and 2 emergency departments in Australia.

Methods: One hundred HIV-uninfected GBM requiring PEP received DTG plus TDF-FTC for 28 days. The primary endpoint was PEP failure (premature PEP cessation or primary HIV infection through Week 12). Additional endpoints were: adherence by self-report (n=98) and pill count (n=55); safety; and plasma drug levels at Day 28.

Results: PEP completion was 90% (95%CI 84% to 96%). Failures (occurring at a median 9 days, IQR 3-16) comprised loss to follow-up (9%) and adverse event resulting in study drug discontinuation (headache, 1%). No participant was found to acquire HIV through Week 12. Adherence to PEP was 98% by self-report and in the 55 participants with corresponding pill count data. The most common clinical adverse events (AEs) were fatigue (26%), nausea (25%), diarrhoea (21%), and headache (10%). There were only four Grade 3-4 subjective AEs. The most common laboratory AE was raised alanine aminotransferase (22%), but there was no case of clinical hepatitis. At Day 28, the mean estimated glomerular filtration rate (eGFR) decrease was 14ml/min/1.73m (SD 17, p=0.001); an eGFR of<60ml/min/1.73m occurred in 3%.

Conclusions: DTG with TDF-FTC is a safe and well-tolerated option for once-daily PEP.

Abstract access

Cure and vaccination – more steps forward in understanding persistence of HIV and how we might deal with it

Editor’s notes: CD32a is the exciting new marker for T-lymphocytes that seem to harbour the reservoir for HIV in peripheral blood. These cells form a very small proportion of all CD4 T-lymphocytes, but they host copies of the virus in their DNA that can be woken up and start replicating again. While this is still a discovery at the level of basic immunology, it raises important possibilities for measuring the reservoir and perhaps for intervening directly to drain it. It may also lead on to further basic biological understanding of why this particular transmembrane protein should be so significantly expressed in latently infected cells but not in bystanders [Descours B et al., Richman DD].
Two papers are relevant to the push for an HIV vaccine. A new mathematical model by Medlock J et al. highlights the potential contribution of a vaccine (or indeed other prevention technologies) over and above the impact of better diagnosis, linkage and treatment of people living with HIV as framed in the 90:90:90 treatment target of UNAIDS. Of course, a significant advantage of a vaccine or a prevention technology is that primary prevention leads to a more rapid reduction in the number of people living with HIV and the associated costs of lifelong ART. UNAIDS strategy already includes a major push for those prevention tools that have been shown to work, with emphasis on combination prevention including structural (such as incentives to keep girls in school and improving access to condoms), behavioural (such as increasing condom usage) and biomedical (such as PrEP) elements within an approach that prioritizes the highest burdened locations and populations. It is not clear that this new model has incorporated these wider prevention programmes in their baseline scenarios. Nonetheless the conclusion is still that we should maintain our enthusiasm for the ongoing and imminent large scale clinical trials of vaccine candidates!

And finally for this month, another encouraging immunotherapy study from NIAID. In a macaque model using a humanized SHIV (a virus that still infects macaques but has been engineered to express HIV proteins), Nishimura Y et al. found a big difference when treatment was stopped between standard ART and infusions of broadly neutralizing antibodies infused around the time of infection. Whereas the viral load rebounded soon after the ART was stopped, several of the macaques were able to continue to suppress the SHIV for up to two years after the infusion of antibodies. The mechanism was shown to be through the CD8 T cell pathway, since removal of these cells led to rapid viral rebound in the antibody treated animals. With each new discovery in the animal and immunology laboratories, we get a little closer to understanding what it might take to develop an effective vaccine that could provide durable protection against HIV or provide effective treatment or therapeutic enhancement that allowed people living with HIV to no longer require ART. That is a goal that we are all pushing towards!

CD32a is a marker of a CD4 T-cell HIV reservoir harbouring replication-competent proviruses.


The persistence of the HIV reservoir in infected individuals is a major obstacle to the development of a cure for HIV. Here, using an in vitro model of HIV-infected quiescent CD4 T cells, we reveal a gene expression signature of 103 upregulated genes that are specific for latently infected cells, including genes for 16 transmembrane proteins. In vitro screening for surface expression in HIV-infected quiescent CD4 T cells shows that the low-affinity receptor for the immunoglobulin G Fc fragment, CD32a, is the most highly induced, with no detectable expression in bystander cells. Notably, productive HIV-1 infection of T-cell-receptor-stimulated CD4 T cells is not associated with CD32a expression, suggesting that a quiescence-dependent mechanism is required for its induction. Using blood samples from HIV-1-positive participants receiving suppressive antiretroviral therapy, we identify a subpopulation of 0.012% of CD4 T cells that express CD32a and host up to three copies of HIV DNA per cell. This CD32a⁺ reservoir was highly enriched in inducible replication-competent proviruses and can be predominant in some participants. Our discovery that CD32a⁺ lymphocytes represent the elusive HIV-1 reservoir may lead to insights that will facilitate the specific targeting and elimination of this reservoir.

Abstract access
HIV: Finding latent needles in a haystack.


Antiretroviral therapy can keep HIV at bay, but a few cells remain infected, so the disease cannot be cured. The discovery of a protein that marks out these infected cells will facilitate crucial studies of this latent viral reservoir.

Abstract access

Effectiveness of UNAIDS targets and HIV vaccination across 127 countries.


The HIV pandemic continues to impose enormous morbidity, mortality, and economic burdens across the globe. Simultaneously, innovations in antiretroviral therapy, diagnostic approaches, and vaccine development are providing novel tools for treatment-as-prevention and prophylaxis. We developed a mathematical model to evaluate the added benefit of an HIV vaccine in the context of goals to increase rates of diagnosis, treatment, and viral suppression in 127 countries. Under status quo interventions, we predict a median of 49 million [first and third quartiles 44M, 58M] incident cases globally from 2015 to 2035. Achieving the Joint United Nations Program on HIV/AIDS 95-95-95 target was estimated to avert 25 million [20M, 33M] of these new infections, and an additional 6.3 million [4.8M, 8.7M] reduction was projected with the 2020 introduction of a 50%-efficacy vaccine gradually scaled up to 70% coverage. This added benefit of prevention through vaccination motivates imminent and ongoing clinical trials of viable candidates to realize the goal of HIV control.

Abstract access

Early antibody therapy can induce long-lasting immunity to SHIV.


Highly potent and broadly neutralizing anti-HIV-1 antibodies (bNAbs) have been used to prevent and treat lentivirus infections in humanized mice, macaques, and humans. In immunotherapy experiments, administration of bNAbs to chronically infected animals transiently suppresses virus replication, which invariably returns to pre-treatment levels and results in progression to clinical disease. Here we show that early administration of bNAbs in a macaque simian/human immunodeficiency virus (SHIV) model is associated with very low levels of persistent viraemia, which leads to the establishment of T-cell immunity and resultant long-term infection control. Animals challenged with SHIVADIEEO by mucosal or intravenous routes received a single 2-week course of two potent passively transferred bNAbs (3BNC117 and 10-1074 (refs 13, 14)). Viraemia remained undetectable for 56-177 days, depending on bNAb half-life in vivo. Moreover, in the 13 treated monkeys, plasma virus loads subsequently declined to undetectable levels in 6 controller macaques. Four additional animals maintained their counts of T cells carrying the CD4 antigen (CD4+) and very low levels of viraemia persisted for over 2 years. The frequency of cells carrying replication-competent virus was less than 1 per 10^6 circulating CD4+ T cells in the six controller macaques. Infusion of a T-cell-depleting anti-CD8β monoclonal antibody to the controller animals led to a specific
decline in levels of CD8+ T cells and the rapid reappearance of plasma viraemia. In contrast, macaques treated for 15 weeks with combination anti-retroviral therapy, beginning on day 3 after infection, experienced sustained rebound plasma viraemia when treatment was interrupted. Our results show that passive immunotherapy during acute SHIV infection differs from combination anti-retroviral therapy in that it facilitates the emergence of potent CD8+ T-cell immunity able to durably suppress virus replication.

Abstract access

3. Key populations

**Stigma and sex work**

*Editor's notes:* Two interesting studies this month looked at aspects of stigma. There are big methodological challenges to the study of stigma. Stigma comprises several different domains and few studies use standardized approaches to measurement that can be translated easily into other contexts. A systematic review and meta-analysis concludes that people who feel more stigmatized are twice as likely to delay presenting for HIV care. Gesesew HA and colleagues found only ten studies that met their pre-specified inclusion criteria, and five of these came from Ethiopia. They acknowledge many of the challenges in combining the results of these ten studies into a single conclusion. They recommend engagement of health care workers to try to reduce perceived stigma among people living with HIV.

The Nyblade L et al. study from Kenya emphasizes the perception of stigma among sex workers. In a large sample of 497 females and 232 males, most reported experiencing stigma both verbal and measured from health care workers. For female sex workers, the anticipation of such stigma led to avoidance of health services for both HIV and non-HIV related conditions. In order to provide effective services for key populations, health care workers must be trained to be non-judgemental. HIV services need to be provided in the context of an overall package of health care.

A study from Europe used ecological data to explore structural risks for HIV among sex workers. Reeves A and colleagues used regression modelling with data on sex work policies from 27 countries. They showed a strong correlation between criminalisation of sex work and higher prevalence of HIV among sex workers. Although they included other factors such as the level of economic development and using drugs, the relatively small number of data points does mean that there may be other confounding factors that could not be measured or adjusted for.

**Significant association between perceived HIV related stigma and late presentation for HIV/AIDS care in low and middle-income countries: A systematic review and meta-analysis.**


Background: Late presentation for human immunodeficiency virus (HIV) care is a major impediment for the success of antiretroviral therapy (ART) outcomes. The role that stigma plays as a potential barrier to timely diagnosis and treatment of HIV among people living with HIV/AIDS (acquired immunodeficiency syndrome) is ambivalent. This review aimed to assess the best available evidence regarding the association between perceived HIV related stigma and time to present for HIV/AIDS care.
Methods: Quantitative studies conducted in English language between 2002 and 2016 that evaluated the association between HIV related stigma and late presentation for HIV care were sought across four major databases. This review considered studies that included the following outcome: 'late HIV testing', 'late HIV diagnosis' and 'late presentation for HIV care after testing'. Data were extracted using a standardized Joanna Briggs Institute (JBI) data extraction tool. Meta-analysis was undertaken using Revman-5 software. I2 and chi-square test were used to assess heterogeneity. Summary statistics were expressed as pooled odds ratio with 95% confidence intervals and corresponding p-value.

Results: Ten studies from low- and middle- income countries met the search criteria, including six (6) and four (4) case control studies and cross-sectional studies respectively. The total sample size in the included studies was 3788 participants. Half (5) of the studies reported a significant association between stigma and late presentation for HIV care. The meta-analytical association showed that people who perceived high HIV related stigma had two times more probability of late presentation for HIV care than who perceived low stigma (pooled odds ratio = 2.4; 95%CI: 1.6-3.6, I2 = 79%).

Conclusions: High perceptions of HIV related stigma influenced timely presentation for HIV care. In order to avoid late HIV care presentation due the fear of stigma among patients, health professionals should play a key role in informing and counselling patients on the benefits of early HIV testing or early entry to HIV care. Additionally, linking the systems and positive case tracing after HIV testing should be strengthened.

Abstract Full-text [free] access

The relationship between health worker stigma and uptake of HIV counseling and testing and utilization of non-HIV health services: the experience of male and female sex workers in Kenya.


The barrier HIV-stigma presents to the HIV treatment cascade is increasingly documented; however less is known about female and male sex worker engagement in and the influence of sex-work stigma on the HIV care continuum. While stigma occurs in all spheres of life, stigma within health services may be particularly detrimental to health seeking behaviors. Therefore, we present levels of sex-work stigma from healthcare workers (HCW) among male and female sex workers in Kenya, and explore the relationship between sex-work stigma and HIV counseling and testing. We also examine the relationship between sex-work stigma and utilization of non-HIV health services. A snowball sample of 497 female sex workers (FSW) and 232 male sex workers (MSW) across four sites was recruited through a modified respondent-driven sampling process. About 50% of both male and female sex workers reported anticipating verbal stigma from HCW while 72% of FSW and 54% of MSW reported experiencing at least one of seven measured forms of stigma from HCW. In general, stigma led to higher odds of reporting delay or avoidance of health services, as well as non-HIV specific services. Statistical significance of relationships varied across type of health service, type of stigma and gender. For example, anticipated stigma was not a significant predictor of delay or avoidance of health services for MSW; however, FSW who anticipated HCW stigma had significantly higher odds of avoiding (OR = 2.11) non-HIV services, compared to FSW who did not. This paper adds to the growing evidence of stigma as a roadblock in the HIV
treatment cascade, as well as its undermining of the human right to health. While more attention is being paid to addressing HIV-stigma, it is equally important to address the key population stigma that often intersects with HIV-stigma.

Abstract access

National sex work policy and HIV prevalence among sex workers: an ecological regression analysis of 27 European countries.


Background: Sex workers are disproportionately affected by HIV compared with the general population. Most studies of HIV risk among sex workers have focused on individual-level risk factors, with few studies assessing potential structural determinants of HIV risk. In this Article, we examine whether criminal laws around sex work are associated with HIV prevalence among female sex workers.

Method: We estimate cross-sectional, ecological regression models with data from 27 European countries on HIV prevalence among sex workers from the European Centre for Disease Control; sex-work legislation from the US State Department's Country Reports on Human Rights Practices and country-specific legal documents; the rule of law and gross-domestic product per capita, adjusted for purchasing power, from the World Bank; and the prevalence of injecting drug use among sex workers. Although data from two countries include male sex workers, the numbers are so small that the findings here essentially pertain to prevalence in female sex workers.

Findings: Countries that have legalised some aspects of sex work (n=17) have significantly lower HIV prevalence among sex workers than countries that criminalise all aspects of sex work (n=10; β=-2.09, 95% CI -0.80 to -3.37; p=0.003), even after controlling for the level of economic development (β=-1.86; p=0.038) and the proportion of sex workers who are injecting drug users (-1.93; p=0.026). We found that the relation between sex work policy and HIV among sex workers might be partly moderated by the effectiveness and fairness of enforcement, suggesting legalisation of some aspects of sex work could reduce HIV among sex workers to the greatest extent in countries where enforcement is fair and effective.

Interpretation: Our findings suggest that the legalisation of some aspects of sex work might help reduce HIV prevalence in this high-risk group, particularly in countries where the judiciary is effective and fair.

Abstract access

4. Health systems and services

Integration of reproductive health and rights

Editor's notes: Integration of reproductive health services and rights needs to be well coordinated with HIV services, so a randomized trial of integration of family planning services into HIV care clinics in Kenya by Cohen CR and colleagues is encouraging. In their initial randomized trial, 12 clinics were randomly selected for early integration using resources from the study team, while six were delayed. Subsequently the Ministry of Health took over the integration and provision of "one stop shop" services at all 18 clinics. The improvements in contraceptive uptake and decreased pregnancy rates
that had been observed in the first phase were maintained during the second phase giving more confidence that it was truly the integrated nature of the services rather than the presence of special study team that had led to the difference.

Another major push for integration or coordination between HIV and sexual and reproductive health and rights services is around the prevention of cervical cancer. Cervical cancer is caused by long-term infection with specific types of human papilloma virus. Women living with HIV are at considerably increased risk of cervical cancer compared to their HIV-negative peers. A large cohort study by Kelly HA et al. in Burkina Faso and South Africa has shown that women living with HIV, attending clinical care services have a high prevalence (59-79% at baseline), incidence (48%) and persistence (up to 70% for some types) of HR-HPV and correspondingly a high prevalence and incidence of cervical neoplasia. There are two HPV vaccines currently available, the first prevents HPV types 16 and 18 (the causes of around 70% of cervical cancer) while the newer (and currently more expensive) vaccine prevents nine types (that cause at least 90% of cervical cancer). HPV vaccination is recommended to be given before sexual debut, as it gives high protection against the specific types of HPV prior to acquisition. The dynamics of the many different types of HPV after acquisition is less clear. The virus is often acquired and they may be cleared or may persist. So this study provides important background data for understanding the possible role of vaccination and also which types are most associated with pre-cancers (cervical Intra-epithelial neoplasia [CIN]) that can be treated and cured relatively easily. In particular, in this study, HPV58, which is in the same (alpha-9) family as HPV16 showed the greatest association with CIN2+. HPV58 is included in the newer nonavalent vaccine, but not the current bi- or quadrivalent vaccine. Overall this is an area where we need more research on the impact of vaccination and screening programmes for women living with HIV, but in the meantime, HPV vaccination for school girls (and boys) is an investment in the future, since these vaccines are effective ways to stop people dying of cervical (and other HPV-related) cancers.

One of the challenges for integrated reproductive services is to continue to emphasize the importance of condoms for protection against HIV and sexually transmitted infections even if other methods are being used for contraception. Such “dual protection” is particularly hard to achieve in married or cohabiting couples despite evidence of ongoing risk of HIV infection. A study in 2388 urban 18-24 year old individuals in Zambia (69% female; 35% married) shows that condom use is still much too low with only 45% reporting that they had used a condom in the last 12 months. As might be anticipated, the study found that the poorest and people who were married were least likely to use condoms while people who discussed contraception and agreed to use condoms were more likely to do so [Pinchoff J et al.] The importance of dual protection, and of promoting broader HIV prevention messages to women through integrated (or at least coordinated) reproductive health and rights services is made even more important given the possibility that depot medroxyprogesterone acetate (DMPA) as a long acting reversible contraceptive may increase the risk of HIV acquisition. WHO has recently changed their guidance to make such contraceptives grade 2 in the Medical Eligibility for Contraceptives (MEC) guidelines.

Integration of family planning services into HIV care clinics: Results one year after a cluster randomized controlled trial in Kenya.

Objectives: To determine if integration of family planning (FP) and HIV services led to increased use of more effective contraception (i.e. hormonal and permanent methods, and intrauterine devices) and decreased pregnancy rates.

Design: Cohort analysis following cluster randomized trial, when the Kenya Ministry of Health led integration of the remaining control (delayed integration) sites and oversaw integrated services at the original intervention (early integration) sites.

Setting: Eighteen health facilities in Kenya.

Subjects: Women aged 18-45 receiving care: 5682 encounters at baseline, and 11,628 encounters during the fourth quarter of year 2.

Intervention: “One-stop shop” approach to integrating FP and HIV services.

Main outcome measures: Use of more effective contraceptive methods and incident pregnancy across two years of follow-up.

Results: Following integration of FP and HIV services at the six delayed integration clinics, use of more effective contraception increased from 31.7% to 44.2% of encounters (+12.5%; Prevalence ratio (PR) = 1.39 (1.19-1.63)). Among the twelve early integration sites, the proportion of encounters at which women used more effective contraceptive methods was sustained from the end of the first to the second year of follow-up (37.5% vs. 37.0%). Pregnancy incidence including all 18 integrated sites in year two declined in comparison to the control arm in year one (rate ratio: 0.72; 95% CI 0.60-0.87).

Conclusions: Integration of FP services into HIV clinics led to a sustained increase in the use of more effective contraceptives and decrease in pregnancy incidence 24 months following implementation of the integrated service model.

Trial registration: ClinicalTrials.gov NCT01001507.

Abstract Full-text [free] access

Associations of human papillomavirus (HPV) genotypes with high-grade cervical neoplasia (CIN2+) in a cohort of women living with HIV in Burkina Faso and South Africa.


Objective: To describe associations of high-risk human papillomavirus (HR-HPV) with high-grade cervical intraepithelial neoplasia (CIN2+) in women living with HIV (WLHIV) in Burkina Faso (BF) and South Africa (SA).

Methods: Prospective cohort of WLHIV attending HIV outpatient clinics and treatment centres. Recruitment was stratified by ART status. Cervical HPV genotyping using INNO-LiPA and histological assessment of 4-quadrant cervical biopsies at enrolment and 16 months later.

Results: Among women with CIN2+ at baseline, the prevalence of any HR-HPV genotypes included in the bi/quadrivalent (HPV16/18) or nonavalent (HPV16/18/31/35/45/52/58) HPV vaccines ranged from 37% to 90%. HPV58 was most strongly associated with CIN2+ (aOR = 5.40, 95%CI: 2.77-10.53). At 16-months follow-up, persistence of any HR-HPV was strongly associated with incident CIN2+ (aOR = 7.90, 95%CI: 3.11-20.07), as was persistence of HPV16/18 (aOR =
Conclusion: HR-HPV persistence is very common among African WLHIV and is linked to incident CIN2+. HPV vaccines could prevent between 37-90% of CIN2+ among African WLHIV.

Abstract Full-text [free] access

Why don’t urban youth in Zambia use condoms? The influence of gender and marriage on non-use of male condoms among young adults.


Background: Zambia experiences high unmet need for family planning and high rates of HIV, particularly among youth. While male condoms are widely available and 95% of adults have heard of them, self-reported use in the past 12 months is low among young adults (45%). This study describes factors associated with non-use of male condoms among urban young adults in Zambia.

Methods: A household cross-sectional survey in four urban districts was conducted from November 2015 to January 2016 among sexually active young adults ages 18-24 years. A random walk strategy was implemented in urban areas; eligible, enrolled participants were administered a survey on household characteristics, health access, and knowledge, attitudes and practices related to contraception. Relative risk regression models were built to determine factors associated with the decision to not use a male condom (non-use) at most recent sexual intercourse.

Results: A total of 2388 individuals were interviewed; 69% were female, 35% were married, and average lifetime sex partners was 3.45 (SD:±6.15). Non-use of male condoms was 59% at most recent sexual intercourse. In a multivariate model, women were more likely to report non-use of a male condom compared with men (aRR = 1.24 [95% CI: 1.11, 1.38]), married individuals were more likely to report non-use compared with unmarried individuals (aRR = 1.59 [1.46, 1.73]), and those residing in the highest poverty wards were more likely to report non-use compared with those in the lowest poverty wards (aRR = 1.31 [1.16, 1.48]). Those with more negative perceptions of male condom use were 6% more likely to report non-use (aRR = 1.06 [1.03, 1.09]). Discussion regarding contraception with a partner decreased non-use 13% (aRR = 0.87 [0.80, 0.95]) and agreement regarding male condom use with a partner decreased non-use 16% (aRR = 0.84 [0.77, 0.91]).

Discussion: Non-use of male condoms is high among young, married adults, particularly women, who may be interested in contraception for family planning but remain at risk of STI infection. Effective marketing strategy of dual protection methods to this population is critical.

Abstract Full-text [free] access

Infectious co-morbidities – why are people still dying of advanced HIV infections?

Editor’s notes: Tuberculosis remains the biggest reported killer of people living with HIV. Studies from Guangxi, China and Nigeria examine risk factors for tuberculosis. In the Chinese study, Cui Z and colleagues found almost one in six of 1019 people receiving care for HIV had active tuberculosis. The risk factors that they found when comparing these 160 people with tuberculosis to matched
controls living with HIV but without tuberculosis were well-known (low CD4 cell count, smoking and non-use of ART). Long duration of HIV infection was also independently associated with developing tuberculosis, emphasising the need for tuberculosis specific measures in addition to ART. The authors recommend standard approaches that need to be strengthened (active screening and case-finding with early initiation of ART; isoniazid preventive therapy and better infection control). The most extraordinary statistic is how much higher the rate of tuberculosis is among this group of people receiving HIV care than it is among the general population of Guangxi. 173 times higher is pretty impressive!

The Pathmanathan I et al. study in Nigeria, carried out as part of a broader analysis of the outcomes of a nationally representative sample of people taking ART, is more optimistic. The incidence rate for tuberculosis once people started on ART was 0.57 per 100 person years, which compares quite favourably with the estimated incidence for Nigeria from the WHO Global Tuberculosis 2016 report [link] of 0.32 per 100 person years. Furthermore, most of the incident tuberculosis occurred soon after starting ART and (as might be expected) was most common in people with low CD4 count; previous tuberculosis or suspected but not diagnosed tuberculosis on starting ART. Once people's CD4 count was above 200 cells per ml, the incidence rate was 0.29 per 100 person-years. This is encouraging, as it suggests that a good ART programme could have a significant impact on the overall risk of tuberculosis. The aim of collaborative tuberculosis and HIV programme efforts must be to find people living with HIV before they are so immunocompromised. In this study, the average CD4 count at enrolment was less than 200 cells per ml and around 5% of people already had tuberculosis at that time.

Late HIV diagnosis was also the subject of a study from Jiangsu province in China. Hu H and colleagues looked at the trends in HIV testing and presentation to care before the CD4 count fell below 350 cells per ml. From 2011-2014 in cross-sectional annual community based surveys among around 2500 men who have sex with men (MSM), there was a modest decline in the proportion who had had an HIV test within the last 12 months from 60% to 53%, and late presentation remained stable around 40%. We have to shift from this plateau and the authors point out that HIV self-tests seem highly acceptable to MSM in China and that social media and internet based advocacy might also help.

There is increasing interest in co-infections with hepatitis B and C viruses in people living with HIV. Hepatitis B is widespread in many countries in sub-Saharan Africa with “horizontal” transmission occurring in childhood. Vaccination is now included as part of some countries programmes on expanded immunisation. Co-infection with HIV and Hepatitis B leads to more rapid progression of liver damage and to liver cancer. Seremba E and colleagues tested stored sera from people living with HIV in the Rakai community and found that around half had already been infected with hepatitis B (in line with the high prevalence of infection in children). During the follow up samples from people who were hepatitis B negative, new infections with hepatitis B occurred in 39 individuals, giving an incidence rate of 1.2 per 100 person years. While hepatitis B vaccine is recommended for people living with HIV who are not infected, this study shows that ART is also protective, particularly if it contains lamivudine or tenofovir. So this may be an added benefit of the wider scale-up of ART.

Despite advance in ART, too many people still die with HIV-associated infections that are only seen at low CD4 cell counts. An important example is cryptococcal meningitis, which causes an insidious onset of symptoms. By the time patients are seen at the hospital with severe headache and signs of raised intracranial pressure it is often too late to prevent them from dying. This is because the best medicines (liposomal amphotericin and flucytosine) are expensive and often not available. So WHO recommends pre-emptive treatment for people who are first seen at the health service with CD4
counts less than 100 cells per ml and with cryptococcal antigen (CRAG) detectable in the blood. A modelling study by Ramachandran A et al. from Uganda and the US considered the likely costs and benefits of using a new lateral flow assay for CRAG for people living with HIV with a low CD4 count, with preemptive treatment with fluconazole for people found to be CRAG-positive. The results, including various sensitivity tests, are strongly in favour of widespread implementation of this strategy. The authors calculate that it would cost Uganda around US$650 000 per year and would avert more than a thousand deaths. Like the tuberculosis discussions above, the real aim is to prevent people living with HIV reaching the stage where “old-fashioned” opportunistic infections can cause such misery. However in the medium term, we are likely to continue to see many people presenting late in the course of their infections, and CRAG (and tuberculosis) screening and management are key ways to prevent mortality.

Risk factors associated with Tuberculosis (TB) among people living with HIV/AIDS: A pair-matched case-control study in Guangxi, China.


Background: As one of the poorest provinces in China, Guangxi has a high HIV and TB prevalence, with the annual number of TB/HIV cases reported by health department among the highest in the country. However, studies on the burden of TB-HIV co-infection and risk factors for active TB among HIV-infected persons in Guangxi have rarely been reported.

Objective: To investigate the risk factors for active TB among people living with HIV/AIDS in Guangxi Zhuang autonomous region, China.

Methods: A surveillance survey was conducted of 1019 HIV-infected patients receiving care at three AIDS prevention and control departments between 2013 and 2015. We investigated the cumulative prevalence of TB during 2 years. To analyze risk factors associated with active TB, we conducted a 1:1 pair-matched case-control study of newly reported active TB/HIV co-infected patients. Controls were patients with HIV without active TB, latent TB infection or other lung disease, who were matched with the case group based on sex and age (±3 years).

Results: A total of 1019 subjects were evaluated. 160 subjects (15.70%) were diagnosed with active TB, including 85 clinically diagnosed cases and 75 confirmed cases. We performed a 1:1 matched case-control study, with 82 TB/HIV patients and 82 people living with HIV/AIDS based on surveillance site, sex and age (±3) years. According to multivariate analysis, smoking (OR = 2.996, 0.992-9.053), lower CD4+ T-cell count (OR = 3.288, 1.161-9.311), long duration of HIV-infection (OR = 5.946, 2.221-15.915) and non-use of ART (OR = 7.775, 2.618-23.094) were independent risk factors for TB in people living with HIV/AIDS.

Conclusion: The prevalence of active TB among people living with HIV/AIDS in Guangxi was 173 times higher than general population in Guangxi. It is necessary for government to integrate control planning and resources for the two diseases. Medical and public health workers should strengthen health education for TB/HIV prevention and treatment and promote smoking cessation. Active TB case finding and early initiation of ART is necessary to minimize the burden of disease among patients with HIV, as is IPT and infection control in healthcare facilities.

Abstract Full-text [free] access


Background: Nigeria had the most AIDS-related deaths worldwide in 2014 (170 000), and 46% were associated with tuberculosis (TB). Although treatment of people living with HIV (PLHIV) with antiretroviral therapy (ART) reduces TB-associated morbidity and mortality, incident TB can occur while on ART. We estimated incidence and characterized factors associated with TB after ART initiation in Nigeria.

Methods: We analyzed retrospective cohort data from a nationally representative sample of adult patients on ART. Data were abstracted from 3496 patient records, and analyses were weighted and controlled for a complex survey design. We performed domain analyses on patients without documented TB disease and used a Cox proportional hazard model to assess factors associated with TB incidence after ART.

Results: At ART initiation, 3350 patients (95.8%) were not receiving TB treatment. TB incidence after ART initiation was 0.57 per 100 person-years, and significantly higher for patients with CD4<50/μL (adjusted hazard ratio [AHR]:4.2, 95% confidence interval [CI]: 1.4-12.7) compared with CD4≥200/μL. Patients with suspected but untreated TB at ART initiation and those with a history of prior TB were more likely to develop incident TB (AHR: 12.2, 95% CI: 4.5-33.5 and AHR: 17.6, 95% CI: 3.5-87.9, respectively).

Conclusion: Incidence of TB among PLHIV after ART initiation was low, and predicted by advanced HIV, prior TB, and suspected but untreated TB. Study results suggest a need for improved TB screening and diagnosis, particularly among high-risk PLHIV initiating ART, and reinforce the benefit of early ART and other TB prevention efforts.

Abstract Full-text [free] access

Trends in late HIV diagnosis among men who have sex with men in Jiangsu province, China: Results from four consecutive community-based surveys, 2011-2014.


Objectives: To examine trends in HIV testing, late HIV diagnosis and associated factors among men who have sex with men (MSM) in Jiangsu province, China.

Methods: Four consecutive community-based cross-sectional surveys were conducted among MSM from 2011 to 2014 in eight cities in the province. Participants were recruited from MSM venues and via the internet. HIV bio-behavioral surveys were conducted to collect demographic and behavioral data and measure HIV infection. HIV-infected participants with CD4 counts less than 350 cells/μL were defined as having a late HIV diagnosis. Chi-square trend tests were used to compare temporal changes over the years and multivariable logistic regression analyses were used to identify factors associated with late diagnosis.

Results: A total of 2441, 2677, 2591 and 2610 participants were enrolled in 2011, 2012, 2013 and 2014, respectively. Testing for HIV in the last 12 months decreased over the time period, from 59.9% to 52.5% (p<0.001). Late HIV diagnosis remained high and steady, ranging from 33.3% to
44.2% over the years with no significant change over time (p = 0.418). MSM who were older than 24 years (aOR =1.748, p = 0.020 for 25-39 years old; aOR = 3.148, p<0.001 for 40 years old or older), were recruited via internet (aOR = 1.596, p = 0.024), and did not have an HIV test in the past 12 months (aOR = 3.385, p<0.001) were more likely to be late diagnosed.

Conclusions: Our study showed a plateau in HIV testing among MSM in China, in parallel to high levels of late diagnosis. Emerging and innovative strategies such as HIV self-testing and reaching more MSM by internet, both highly acceptable to MSM in China, may reduce late diagnosis.

Abstract

Hepatitis B incidence and prevention with antiretroviral therapy among HIV-positive individuals in Uganda.


Objective: Antiretroviral therapy (ART) may interfere with replication of hepatitis B virus (HBV), raising the hypothesis that HBV infection might be prevented by ART. We investigated the incidence and risk factors associated with HBV among HIV-infected adults in Rakai, Uganda.

Methods: We screened stored sera from 944 HIV-infected adults enrolled in the Rakai Community Cohort Study between September 2003 and March 2015 for evidence of HBV exposure. Serum from participants who tested anti-hepatitis B core-negative (497) at baseline were tested over 3-7 consecutive survey rounds for incident HBV. Poisson incidence methods were used to estimate incidence of HBV with 95% confidence intervals (CIs), whereas Cox proportional regression methods were used to estimate hazard ratios (HRs).

Results: Thirty-nine HBV infections occurred over 3342 person-years, incidence1.17/100 person-years. HBV incidence was significantly lower with ART use: 0.49/100 person-years with ART and 2.3/100 person-years without ART [adjusted HR (aHR) 0.25, 95% CI 0.1-0.5, P<0.001], and with lamivudine (3TC) use: (0.58/100 person-years) with 3TC and 2.25/100 person-years without 3TC (aHR 0.32, 95% CI0.1-0.7, P= <0.007). No new HBV infections occurred among those on tenofovir-based ART. HBV incidence also decreased with HIV RNA suppression: 0.6/100 person-years with 400copies/ml or less and 4.0/100 person-years with more than 400copies/ml (aHR, 6.4, 95% CI 2.2-19.0, P<0.001); and with age: 15-29 years versus 40-50 years (aHR 3.2, 95% CI 1.2-9.0); 30-39 years versus 40-50 years (aHR 2.1, 95% CI 0.9-5.3).

Conclusion: HBV continues to be acquired in adulthood among HIV-positive Ugandans and HBV incidence is dramatically reduced with HBV-active ART. In addition to widespread vaccination, initiation of ART may prevent HBV acquisition among HIV-positive adults in sub-Saharan Africa.

Abstract access

Cost-effectiveness of CRAG-LFA screening for cryptococcal meningitis among people living with HIV in Uganda.


Background: Cryptococcal meningitis (CM) constitutes a significant source of mortality in resource-limited regions. Cryptococcal antigen (CRAG) can be detected in the blood before onset of meningitis.
We sought to determine the cost-effectiveness of implementing CRAG screening using the recently developed CRAG lateral flow assay in Uganda compared to current practice without screening.

Methods: A decision-analytic model was constructed to compare two strategies for cryptococcal prevention among people living with HIV with CD4 < 100 in Uganda: No cryptococcal screening vs. CRAG screening with WHO-recommended preemptive treatment for CRAG-positive patients. The model was constructed to reflect primary HIV clinics in Uganda, with a cohort of HIV-infected patients with CD4 < 100 cells/µL. Primary outcomes were expected costs, DALYs, and incremental cost-effectiveness ratios (ICERs). We evaluated varying levels of programmatic implementation in secondary analysis.

Results: CRAG screening was considered highly cost-effective and was associated with an ICER of $6.14 per DALY averted compared to no screening (95% uncertainty range: $-20.32 to $36.47). Overall, implementation of CRAG screening was projected to cost $1.52 more per person, and was projected to result in a 40% relative reduction in cryptococcal-associated mortality. In probabilistic sensitivity analysis, CRAG screening was cost-effective in 100% of scenarios and cost saving (ie cheaper and more effective than no screening) in 30% of scenarios. Secondary analysis projected a total cost of $651,454 for 100% implementation of screening nationally, while averting 1228 deaths compared to no screening.

Conclusion: CRAG screening for PLWH with low CD4 represents excellent value for money with the potential to prevent cryptococcal morbidity and mortality in Uganda.

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