Welcome to the 9th issue of HIV this month in 2017! In this issue, we cover the following topics:

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UNAIDS
1. HIV testing and treatment

Although people living with HIV should have near normal life expectancy, far too many still die prematurely

Editor’s notes: The scale up of antiretroviral therapy is the most important development in the past decade of the HIV response. Not only do antiretroviral medicines prevent death and prevent the immune destruction that HIV causes, but they also prevent transmission to sexual partners. Nonetheless, the challenges of reaching everyone living with HIV are enormous and Young and colleagues’ study from the city of Nairobi highlights that we still have some distance to go. The authors estimated that 74% of adults living with HIV were receiving ART and among women, the figure was even higher and was estimated to have reached more than the UNAIDS target of 81%. The authors collected data from the two largest mortuaries in Nairobi, where most deaths that occur in the city are registered. With approximately 80% of all deaths in the city being registered, the authors believe that their study is reasonably representative of the adult population of the city. They found that among 807 people who died in Nairobi during the recruitment period, HIV was greatly over-represented. They calculated that around 16% of adult deaths in the city were attributable to HIV, and that, when adjusted for age and sex, death rates among people living with HIV were more than four times higher than the rate among HIV-negative people. The authors point out that these proportions and rates are much lower than they were at the peak of the epidemic, but they do show that in Nairobi we still have some distance to go to ensure that people living with HIV have the same life expectancy as those who are HIV-negative.

HIV-associated mortality in the era of antiretroviral therapy scale-up – Nairobi, Kenya, 2015


Background: Declines in HIV prevalence and increases in antiretroviral treatment coverage have been documented in Kenya, but population-level mortality associated with HIV has not been directly measured. In urban areas where a majority of deaths pass through mortuaries, mortuary-based studies have the potential to contribute to our understanding of excess mortality among HIV-infected persons. We used results from a cross-sectional mortuary-based HIV surveillance study to estimate the association between HIV and mortality for Nairobi, the capital city of Kenya.

Methods and Findings: HIV seropositivity in cadavers measured at the two largest mortuaries in Nairobi was used to estimate HIV prevalence in adult deaths. Model-based estimates of the HIV-infected and uninfected population for Nairobi were used to calculate a standardized mortality ratio and population-attributable fraction for mortality among the infected versus uninfected population. Monte Carlo simulation was used to assess sensitivity to epidemiological assumptions. When standardized to the age and sex distribution of expected deaths, the estimated HIV positivity among adult deaths aged 15 years and above in Nairobi was 20.9% (95% CI 17.7-24.6%). The standardized mortality ratio of deaths among HIV-infected versus uninfected adults was 4.35 (95% CI 3.67-5.15), while the risk difference was 0.016 (95% CI 0.013-0.019). The HIV population attributable mortality fraction was 0.161 (95% CI 0.131-0.190). Sensitivity analyses demonstrated robustness of results.
Conclusions: Although 73.6% of adult PLHIV receive antiretrovirals in Nairobi, their risk of death is four-fold greater than in the uninfected, while 16.1% of all adult deaths in the city can be attributed to HIV infection. In order to further reduce HIV-associated mortality, high-burden countries may need to reach very high levels of diagnosis, treatment coverage, retention in care, and viral suppression.

Abstract Full-text [free] access

**Excessive cardiovascular morbidity and mortality among people living with HIV – preventable with better services?**

*Editor’s notes:* Opportunities to prevent mortality among people living with HIV also include careful attention to risk factors for modifiable cardiovascular health risk factors such as smoking, cholesterol levels, weight and exercise. In an interesting study from Canada, Jeon and colleagues used the Ontario administrative databases to look at differences between 259,475 people being admitted with acute myocardial infarction according to their HIV status. Overall, people living with HIV who had heart attacks were around 15 years younger and more than twice as likely to die within 30 days following discharge from the hospital compared to HIV-negative people. This was not because people living with HIV had received care that was obviously different, with similar rates of revascularisation procedures and follow up visits to the cardiology services. The study highlights the ongoing uncertainty about the reasons for increased morbidity and mortality among people living with HIV. However, it is clear that we do have several well proven tools with which to reduce cardiovascular morbidity, so we should ensure that they are incorporated into HIV treatment services.

The relationship between known indicators of cardiovascular risk and HIV were also studied in 67 black South Africans living with HIV. Borkum and colleagues demonstrate that HIV infection in black South Africans living with HIV was generally well controlled with 84% being virally suppressed and that they had a median CD4 count of over 500 cells per microlitre. Nonetheless, most had a variety of characteristics that suggest that they were at high risk of cardiovascular events. Markers of inflammation were raised in 68% and “non-dipping” blood pressure, which is a measure of excessive stiffness of the arteries, was present in 65%. Straightforward measures that could be made even at the most peripheral ART clinic also demonstrated risk, with 67% being classified as overweight and 76% having an increased waist circumference, both well recognized independent risk factors for cardiovascular disease. Worryingly this sample, which was largely female (91%), had an average age of only 42 years. It is clear that intervention on cardiovascular risks is something for all ART providers to consider in every setting.

The Australian Positive and Peers Longevity Evaluation study (beautifully given the acronym of APPLES) also points out the importance of making valid comparisons between people living with HIV and their HIV negative peers. In Australia, almost half of all people living with HIV are now over the age of 50 years. Petoumenos and colleagues show that among gay and bisexual men older than 55 years, recruited in Sydney, those living with HIV were more likely to report noncommunicable comorbidities including heart disease and diabetes. However, some of the more obvious risk factors, such as smoking status, were not different between the groups and people living with HIV drank less alcohol than their HIV negative peers. The relationships between HIV, lifestyle and noncommunicable disease risk are complex but probably important as the population of people living with HIV continues to age.
In a study from the Cohorte de la Red de Investigación en Sida (CoRIS) in Spain, Masiá and colleagues have also explored long term outcomes of almost 9000 people living with HIV and their experience of non-AIDS defining events. They show that mortality rates are considerably higher in people living with HIV who have any non-AIDS event, even if these are traditionally considered less severe, such as bacterial pneumonia, psychiatric diseases, bone fractures, or diabetes. In addition to standard indicators (such as low CD4 count at ART initiation), we should take the development of non-AIDS events as a warning to intensify management efforts and more targeted prevention of complications.

In the UK, Molloy and colleagues conducted an audit of clinical services provided at different sites. They show that systems need to catch up with the changes in life experience of people living with HIV. While sexual health screening was almost universally available, only 71.4% of sites were able to offer cervical cytology despite the increased risk of cervical cancer in women living with HIV. Less than half of people taking ART had their risk for cardiovascular disease documented. Regular audit of appropriate services, even with simple checklists for service providers is a strong tool to improve care for people living with HIV and should have a direct impact on mortality.

Mortality and health service use following acute myocardial infarction among persons with HIV: a population-based study


People with HIV have higher rates of acute myocardial infarction (AMI) than HIV-negative individuals. We compared mortality risk and health service use following AMI among people with and without HIV between January 1, 2002, and March 31, 2015. We conducted a population-based study using Ontario’s administrative databases. Our primary outcomes were risk of inpatient death and death at 30 days following hospital discharge. In secondary analyses, we compared use of revascularization procedures within 90 days of AMI, as well as readmission or emergency department visits for heart disease and cardiology follow-up within 90 days of discharge. We studied 259 475 AMI patients, of whom 345 (0.13%) were people with HIV. AMI patients with HIV were younger than HIV-negative patients (mean age ± standard deviation: 54.4 ± 10.5 years vs. 69.3 ± 14.3 years). Following multivariable adjustment, the odds ratios for inpatient death and death at 30 days following discharge were 1.04 [95% confidence intervals (CI) 0.64-1.56] and 2.42 (95% CI 1.00-4.92), respectively. In secondary analyses, no differences were observed in receipt of revascularization procedures (hazard ratio (HR) 0.98; 95% CI 0.85-1.12), readmission or emergency department visit for heart disease (HR 1.18; 95% CI 0.85-1.62), or cardiology follow-up (HR 0.88; 95% CI 0.76-1.01). People with HIV experience AMI at younger ages and may be at higher risk of death in the 30 days following hospital discharge, underscoring the importance of targeting modifiable cardiovascular disease risk factors in these patients.

Abstract access

High prevalence of "non-dipping" blood pressure and vascular stiffness in HIV-infected South Africans on antiretrovirals

Background: HIV-infected individuals are at increased risk of tissue inflammation and accelerated vascular aging ("inflamm-aging"). Abnormal diurnal blood pressure (BP) rhythms such as non-dipping may contribute to an increased risk of cardiovascular and cerebrovascular events in HIV infected individuals. However, little data exists on ambulatory blood pressure (ABP) and measures of vascular stiffness in the black African HIV infected population.

Methods: This is a cross-sectional analysis of otherwise well, HIV infected outpatients on ART for >5 years. Study assessments included: 24hr ABP monitoring, pulse wave velocity (PWV) and central aortic systolic pressure (CASP) using a AtCor Medical SphygmoCor device, fasting lipogram, oral glucose tolerance test, high-sensitivity C-reactive protein (hsCRP) and anthropometric data. Patients completed a questionnaire of autonomic symptoms. CD4+ counts and viral loads were obtained from the National Laboratory results system.

Results: Sixty-seven black participants were included in the analysis of whom 91% (n = 61) were female with a mean age of 42.2 ± 8.6 years. The median duration on ART was 7.5 years (IQR = 6-10), 84% were virally supressed and the median CD4 count was 529.5cells/mm³ (IQR = 372.0-686.5). The majority (67%) were classified as overweight and 76% had an increased waist circumference, yet only 88% of participants were normotensive. A hsCRP level in the high cardiovascular risk category was found in 68% of participants. The prevalence of non-dipping BP was 65%. Interestingly, there was no association on multivariable analysis between dipping status and traditional risk factors for non-dipping BP, such as: obesity, autonomic dysfunction and older age.

Conclusion: This relatively young cross-sectional sample of predominantly normotensive, but overweight black women on effective ART >5 years showed: a high prevalence of non-dipping BP, inflammation and vascular stiffness. Causality cannot be inferred but cardiovascular risk reduction should be emphasized in these patients.

Prevalence of self-reported comorbidities in HIV positive and HIV negative men who have sex with men over 55 years—The Australian Positive & Peers Longevity Evaluation Study (APPLES)


In Australia, almost half of HIV-positive people are now aged over 50 and are predominately gay and bisexual men (GBM). Compared to the general HIV-negative population, GBM engage more in behaviours that may increase the risk of age-related comorbidities, including smoking, high alcohol consumption and recreational drug use. The objective of APPLES was to compare comorbidities and risk factors in HIV-positive older GBM with an appropriate control group of HIV-negative GBM. We undertook a prospectively recruited cross-sectional sample of HIV-positive and HIV-negative GBM ≥ 55 years. Detailed data collection included clinic data, a health and lifestyle survey, and blood sample collection. We report key demographic, laboratory markers and self-reported comorbidities by HIV status. For selected comorbidities we also adjust HIV status a priori for age, smoking and body mass index. Over 16 months 228 HIV-positive and 218 HIV-negative men were recruited. Median age was 63 years (IQR: 59-67). Although more HIV-positive men reported having ever smoked, smoking status was not statistically different between HIV positive and HIV negative men (p = 0.081). Greater alcohol use was reported by HIV-negative
men (p = 0.002), and recreational drug use reported more often by HIV-positive men (p<0.001). After adjustment, **HIV-positive men had significantly increased odds of diabetes** (adjusted Odds ratio (aOR): 1.97, p = 0.038), **thrombosis** (aOR: 3.08, p = 0.007), **neuropathy** (aOR: 34.6, P<0.001), and **non-significantly increased odds for heart-disease** (aOR: 1.71, p = 0.077). In conclusion, HIV-positive GBM have significantly increased odds for key self-reported comorbidities. This study underscores the importance of an appropriate HIV-negative control group for more accurate evaluation of the risk and attribution of age-related comorbidities in HIV-positive people.

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

**Prediction of long-term outcomes of HIV-infected patients developing non-AIDS events using a multistate approach**


Objectives: Outcomes of people living with HIV (PLWH) developing non-AIDS events (NAEs) remain poorly defined. **We aimed to classify NAEs according to severity, and to describe clinical outcomes and prognostic factors after NAE occurrence using data from CoRIS, a large Spanish HIV cohort from 2004 to 2013.**

Design: **Prospective multicenter cohort study.**

Methods: **Using a multistate approach we estimated 3 transition probabilities:** from alive and NAE-free to alive and NAE-experienced ("NAE development"); from alive and NAE-experienced to death ("Death after NAE"); and from alive and NAE-free to death ("Death without NAE"). We analyzed the effect of different covariates, including demographic, immunologic and virologic data, on death or NAE development, based on estimates of hazard ratios (HR). We focused on the transition "Death after NAE".

Results: **8789 PLWH were followed-up until death, cohort censoring or loss to follow-up. 792 first incident NAEs occurred in 9.01% PLWH (incidence rate 28.76; 95% confidence interval [CI], 26.80-30.84, per 1000 patient-years). 112 (14.14%) NAE-experienced PLWH and 240 (2.73%) NAE-free PLWH died.** Adjusted HR for the transition "Death after NAE" was 12.1 (95%CI, 4.90-29.89). There was a graded increase in the adjusted HRs for mortality according to NAE severity category:

- **Male sex** (HR 2.04; 95% CI, 1.11-3.84), **age >50 years** (1.78, 1.08-2.94), **hepatitis C-coinfection** (2.52, 1.38-4.61), **lower CD4 cell count at cohort entry** (HR 2.49; 95%CI 1.20-5.14 for CD4 cell count below 200 and HR 2.16; 95%CI 1.01-4.66 for CD4 cell count between 200-350, both compared to CD4 cell count higher than 500) and **concomitant CD4 <200 cells/mL** (2.22, 1.42-3.44) were associated with death after NAE. CD4 count and HIV-1 RNA at engagement, previous AIDS and hepatitis C-coinfection predicted mortality in NAE-free persons.

Conclusion: **NAEs, including low-severity events, increase prominently the risk for mortality in PLWH.** Prognostic factors differ between NAE-experienced and NAE-free persons. These findings should be taken into account in the clinical management of PLWH developing NAEs and may permit more targeted prevention efforts.
Routine monitoring and assessment of adults living with HIV: results of the British HIV Association (BHIVA) national audit 2015


Background: The clinical care of people living with HIV changed fundamentally as a result of the development of effective antiretroviral therapy (ART). HIV infection is now a long-term treatable condition. We report a national audit to assess adherence to British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals.

Methods: All UK sites known as providers of adult HIV outpatient services were invited to complete a case-note review and a brief survey of local clinic practices. Participating sites were asked to randomly select 50-100 adults, who attended for specialist HIV care during 2014 and/or 2015. Each site collected data electronically using a self-audit spreadsheet tool. This included demographic details (gender, ethnicity, HIV exposure, and age) and whether 22 standardised and pre-defined clinical audited outcomes had been recorded.

Results: Data were collected on 8258 adults from 123 sites, representing approximately 10% of people living with HIV reported in public health surveillance as attending UK HIV services. Sexual health screening was provided within 96.4% of HIV services, cervical cytology and influenza vaccination within 71.4% of HIV services. There was wide variation in resistance testing across sites. Only 44.9% of patients on ART had a documented 10-year CVD risk within the past three years and fracture risk had been assessed within the past three years for only 16.7% patients aged over 50 years.

Conclusions: There was high participation in the national audit and good practice was identified in some areas. However, improvements can be made in monitoring of cardiovascular risk, bone and sexual health.

Abstract Full-text [free] access

2. Combination prevention

HIV incidence – labour intensive to measure but key to inform effective HIV prevention programmes

Editor’s notes: It is increasingly clear that in order to control the HIV epidemic, we need to invest not only in the scale up of treatment but also in effective and evidence based prevention programming. UNAIDS has set ambitious targets to reduce the number of new HIV infections to 500 000 by the end of 2020. A major, ongoing, challenge is that we must use mathematical models to estimate the number of new infections. We do not have enough data on the actual number of new infections and the characteristics of the people newly infected. So the household surveys conducted in Rwanda by Nsanzimana and colleagues are an important study. The authors conducted two nationally representative surveys in 2013 and 2014, and were able to repeat HIV tests in 12 593 people out of 13 728 whose initial test had been negative. They found 35 people who had seroconverted, which reminds us how large this sort of study needs to be in a setting where HIV prevalence is around 3%.
The incidence rate of 0.27 per 100 person-years (95% CI: 0.18 – 0.35), is higher than the authors had anticipated from previous modelled estimates. Part of the reason for this was that they found several villages and households with multiple seroconversions, which suggests multiple outbreaks. This heterogeneity in the pattern of new HIV infections could have important implications for prevention activities and approaches, as well as for methodologies used in designing surveys. In Rwanda, the risks of HIV infection were higher among older adults (aged 36-45 years) compared to the younger participants (aged 16-25 years); higher in the West of the country and higher in urban areas. However, the small number of seroconversion events means that the confidence intervals for these comparisons are wide, particularly given the observed heterogeneity between villages in the sample.

Household survey of HIV incidence in Rwanda: a national observational cohort study

Background: In Rwanda, HIV prevalence among adults aged 15-49 years has been stable at 3% since 2005. The aim of this study was to characterise HIV incidence across Rwanda.

Methods: We did a nationally representative, prospective HIV incidence survey for the period of 2013-14, which used two-stage sampling. We randomly selected 492 villages in the first sampling stage and 14 households per village in the second stage. Participants completed a questionnaire and 14 140 people were tested for HIV. 13 728 participants were HIV negative, and were enrolled in the incidence cohort. Participants were retested and surveyed again after 12 months. Weights were calculated as the inverse of the probability to select the villages and the households.

Findings: The study period was from Nov 5, 2013, to Nov 15, 2014. Among 14 222 respondents from 6792 households, 14 140 were tested for HIV and 13 728 were HIV negative. Of 12 593 people who participated in the endpoint data collection activities, 5965 (47·4%) were men and the mean age was 30 years (SD 10·8). 11 237 (89·2%) participants lived in rural areas, 4826 (38·3%) were single, and 7140 (56·7%) were married or cohabitating. During the year, 35 participants had seroconversion, including 13 men and 22 women, resulting in an overall incidence of 0·27 per 100 person-years (95% CI 0·18–0·35). Incidence was 0·21 per 100 person-years (0·10–0·32) in men and 0·32 per 100 person-years (0·19–0·45) in women. Our findings suggested multiple breakouts, with multiple seroconversions occurring in three villages and two households. Incidence was higher in adults aged 36-45 years (0·37 per 100 person-years, 0·12–0·62; adjusted hazard ratio [aHR] 4·49, 95% CI 1·30–14·70) relative to those aged 16-25, higher in western province (0·57 per 100 person-years, 0·31–0·87; aHR 5·90, 1·33–25·28) relative to the northern province, and higher in urban areas (0·65 per 100 person-years, 0·23–1·07; aHR 3·10, 1·28–6·99) than in rural areas.

Interpretation: The incidence of HIV in Rwanda was higher than that previously estimated from models, with outbreaks seeming to contribute to the ongoing epidemic. Characterisation of incident infections can help the national HIV programmes to plan for preventive interventions tailored to the most at-risk populations.

Abstract access

Exciting biomedical advances – keep your eyes on the longer-term opportunities for HIV prevention and treatment
**Editor’s notes:** An important advance on the road to effective immune therapies may have been published in the journal *Science*. We have now entered the era of antibodies for the prevention, and possibly the treatment of HIV. The AMP study is the first large scale study of antibodies being used to try to prevent HIV infection. However, most researchers agree that just like antiretroviral therapy, a cocktail of different antibodies is likely to be needed to prevent HIV escaping from immune control, just as it does from individual medicines. Xu and colleagues at Sanofi have managed to engineer a molecule that is an antibody except that instead of having a single specific target antigen, had three different targets. In other words, it might function as a cocktail despite being a single agent. This is important because it might speed up the critical pathway for research. With multiple antibodies, the regulators naturally want to be certain that each of them is safe and effective before approving trials that combine them. This can take many years, despite the researchers predicting that the single antibody studies are proofs of concept on the longer pathway to a combination that might make a real difference to treatment or prevention programmes. In studies in macaques, the novel tri-specific antibody molecule provided complete immunity to infection with a range of simian-human immunodeficiency viruses (SHIVs), whereas single antibodies only protected against some of the SHIVs. This approach to immunotherapy is also an example of HIV science leading to discoveries that might have a much wider field of application in other diseases such as cancer and autoimmune disease.

In addition to making the best antibodies (or T-cell responses), a vaccine also must deliver the antigen or DNA in such a way that the antibodies are made effectively and in high concentrations by the host’s cells. This is done by means of the vaccine vector. Previous HIV vaccine candidates have had to be withdrawn from the research pipeline because their vectors appear to have caused harm, possibly by stimulating the immune system in such a way that HIV replication was actually enhanced. So, the study by Capucci and colleagues is a useful example to show how different vectors work in animal models. In this study, two vectors that are usually utilized to stimulate T-cell responses were used. A non-replicating chimpanzee adenovirus or a non-replicating modified vaccinia virus Ankara both produced good antibody responses using an HIV glycoprotein trimer that is known to produce neutralizing antibodies. The implication might be that these vectors could carry antigens that could provoke useful antibody responses in addition to useful T-cell responses, thus mimicking the most likely way that HIV is controlled in the human host.

Many studies of new biomedical approaches to HIV prevention are tested first in animal models. Many of us know little of the details of these models. In order to compare different prevention technologies, it is important that the same or comparable models are used. Many studies now use simian-human immunodeficiency virus (SHIV). This is a virus that is genetically modified so that it expresses many aspects of HIV, but still has enough of the SIV components to infect monkeys. SHIV is often inserted into the vagina of rhesus macaques that have been treated with a new prevention technology or a control to determine whether the technology prevents the establishment of infection. In the past most macaques used for this research were from India. However, there is now a shortage of such laboratory monkeys, so Veazey and Ling have done a simple comparison of Indian macaques with Chinese macaques. With this particular common laboratory strain of SHIV, the authors found no important differences between the two sub-species.

Delving further into the comparative immunology of macaques and humans, Fu and colleagues have performed a comprehensive profiling of lymphocyte receptors from a Chinese macaque. These sorts of studies allow vaccine scientists to understand how immune responses in macaques can generate antibody and T-cell responses. They are a building block for future development of vaccines and immune based therapies. And they remind us how advanced the technology is becoming for ever
more detailed understanding of the interactions between primates' immune systems and the environment to which these systems are exposed.

Trispecific broadly neutralizing HIV antibodies mediate potent SHIV protection in macaques

The development of an effective AIDS vaccine has been challenging because of viral genetic diversity and the difficulty of generating broadly neutralizing antibodies (bnAbs). We engineered trispecific antibodies (Abs) that allow a single molecule to interact with three independent HIV-1 envelope determinants: the CD4 binding site, the membrane-proximal external region (MPER), and the V1V2 glycan site. Trispecific Abs exhibited higher potency and breadth than any previously described single bnAb, showed pharmacokinetics similar to those of human bnAbs, and conferred complete immunity against a mixture of simian-human immunodeficiency viruses (SHIVs) in nonhuman primates, in contrast to single bnAbs. Trispecific Abs thus constitute a platform to engage multiple therapeutic targets through a single protein, and they may be applicable for treatment of diverse diseases, including infections, cancer, and autoimmunity.

Abstract Full-text [free] access

HIV-1-neutralizing antibody induced by simian adenovirus- and poxvirus MVA-vectored BG505 native-like envelope trimers

Rabbits and monkeys immunized with HIV type 1 (HIV-1) native-like BG505 SOSIP.664 (BG505s) glycoprotein trimers are known to induce antibodies that can neutralize the autologous tier-2 virus. Here, we assessed the induction of HIV-1 trimer binding and neutralizing antibody (nAb) titres when BG505s trimers were also delivered by non-replicating simian (chimpanzee) adenovirus and non-replicating poxvirus modified vaccinia virus Ankara (MVA) vaccine vectors. First, we showed that approximately two-thirds and one-third of the trimers secreted from the ChAdOx1.BG505s (C) and MVA.BG505s (M) vaccine-infected cells, respectively, were cleaved and in a native-like conformation. Rabbits were immunized intramuscularly with these vaccine vectors and in some cases boosted with ISCOMATRIX™-adjuvanted BG505s protein trimer (P), using CCC, MMM, PPP, CPP, MPP and CMP vaccine regimens. We found that the peak trimer-binding antibody and tier-1A and autologous tier-2 nAb responses induced by the CC, CM, PPP, CPP, MPP and CMP regimens were comparable, although only PPP induced autologous tier-2 nAbs in all the immunized animals. Three animals developed weak heterologous tier-2 nAbs. These results demonstrate that ChAdOx1 and MVA vectors are useful delivery modalities for not only T-cell, but also antibody vaccine development.

Abstract Full-text [free] access
Comparative susceptibility of rhesus macaques of Indian and Chinese origin to vaginal SHIV transmission as models for HIV prevention research


Historically, Indian origin rhesus macaques (iRM) have been preferred for SIV/HIV prevention, pathogenesis, and treatment studies, yet their supply is limited. Chinese origin rhesus macaques (cRM) are currently more available yet little is known regarding the relative susceptibility of this subspecies to vaginal transmission of SIV or SHIV. Here we compared the susceptibility of 40 cRM and 21 iRM to a single vaginal challenge with SHIVsf162P. Our results showed cRM have comparable primary SHIV infection as iRM, underscoring their equal importance in studies of HIV transmission and prevention.

Abstract access

A comprehensive profiling of T- and B-lymphocyte receptor repertoires from a Chinese-origin rhesus macaque by high-throughput sequencing


Due to the close genetic background, high similarity of physiology, and susceptibility to infectious and metabolic diseases with humans, rhesus macaques have been widely used as an important animal model in biomedical research, especially in the study of vaccine development and human immune-related diseases. In recent years, high-throughput sequencing based immune repertoire sequencing (IR-SEQ) has become a powerful tool to study the dynamic adaptive immune responses. Several previous studies had analyzed the responses of B cells to HIV-1 trimer vaccine or T cell repertoire of rhesus macaques using this technique, however, there are little studies that had performed a comprehensive analysis of immune repertoire of rhesus macaques, including T and B lymphocytes. Here, we did a comprehensive analysis of the T and B cells receptor repertoires of a Chinese rhesus macaque based on the 5’-RACE and IR-SEQ. The detailed analysis includes the distribution of CDR3 length, the composition of amino acids and nucleotides of CDR3, V, J and V-J combination usage, the insertion and deletion length distribution and somatic hypermutation rates of the framework region 3 (FR3). In addition, we found that several positions of FR3 region have high mutation frequencies, which may indicate the existence of new genes/alleles that have not been discovered and/or collected into IMGT reference database. We believe that a comprehensive profiling of immune repertoire of rhesus macaque will facilitate the human immune-related diseases studies.

Abstract Full-text [free] access

3. Key populations

Efforts to understand commercial and transactional sex – involve the community and use both quantitative and qualitative methods

Editor’s notes: As the overall number of new HIV infections falls, it is likely that an increasingly large proportion of infections will occur in key populations and among those left behind by HIV services. In
order to plan, deliver, monitor and evaluate services for specific populations, we need to develop the best estimates possible of the number of people in each population. Sharifi and colleagues provide an excellent introduction to some of the methods that have been tried to estimate population size of key populations. Each of the three methods that the authors used to estimate the number of female sex-workers living in urban areas of Iran has strengths and weaknesses. Used together the methods may allow some triangulation of estimates. The authors found that the ‘wisdom of the crowds’, in which sex-workers are asked to provide their own best estimates tended to give the highest figures. The possibility is that where sex work is highly stigmatized and criminalized (as it is in Iran) women may tend to subconsciously exaggerate the numbers in order to normalize their position in society. Multiplier methods which use “capture-recapture” approaches gave the lowest estimates, which may be due to the same sample of women being seen in both the two approaches used to estimate numbers. For instance, if some women are more reluctant to be identified, they may be missed both in the distribution of “tags” or gifts and then again in the “re-capture” survey. The total estimate is then calculated by multiplying the inverse of the proportion of how many women in the survey had received the “tags”. So, this may produce an underestimate if the same women are missed in both rounds of the research. Finally, the network methods are used during national surveys and ask respondents to identify how many of their network are sex workers. Supposedly this avoids the stigma of identifying oneself as a sex worker to the interviewer. The authors best estimate is that there are more than 200 000 female sex workers in urban settings in Iran, which is considerably higher than the previous estimates. However, the paper’s key strength is the discussion of the different approaches and how we can improve our understanding of this valuable metric.

The Iranian researchers used a standard definition of sex work, based on having exchanged sex (vaginal, anal, or oral) for money, goods, or favours with at least one male partner in the past 12 months. However, it is clear that this definition overlaps with many sexual relationships that neither partner would classify as sex work. Raganathan and colleagues present a fascinating qualitative study of transactional sex and sexual agency among young women in rural South Africa. Of course, it is not surprising that sex is embedded within a complex framework of romantic relationships that are modified by the degree to which young women values herself and her own agency. Financial independence is a key to safer relationships, but gifts and money also enhance the status of young women and indicate commitment from their male partner. It is one thing to count and label sexual transactions, but it is another to understand them and work with young people to enhance their ability to avoid HIV infection.

Population size estimation of female sex workers in Iran: synthesis of methods and results

Introduction: Estimating the number of key populations at risk of HIV is essential for planning, monitoring, and evaluating prevention, care, and treatment programmes. **We conducted this study to estimate the number of female sex workers (FSW) in major cities of Iran.**

Methods: **We used three population size estimation methods** (i.e., wisdom of the crowds, multiplier method, and network scale-up) **to calculate the number of FSW in 13 cities in Iran. The wisdom of the crowds and multiplier methods were integrated into a nationwide bio-behavioural surveillance survey in 2015, and the network scale-up method was included in a national survey of the general population in 2014.** The median of the three methods was used to calculate the proportion of the adult female population who practice sex work in the 13 cities.
These figures were then extrapolated to provide a national population size estimation of FSW across urban areas.

Results: The population size of FSW was 91,500 (95% Uncertainty Intervals [UIs] 61,400-117,700), corresponding to 1.43% (95% UIs 0.96-1.84) of the adult (i.e., 15-49 years-old) female population living in these 13 cities. The projected numbers of FSW for all 31 provincial capital cities were 130,800 (95% UIs 87,800-168,200) and 228,700 (95% UIs 153,500-294,300) for all urban settings in Iran.

Conclusions: Using methods of comparable rigor, our study provided a data-driven national estimate of the population size of FSW in urban areas of Iran. Our findings provide vital information for enhancing HIV programme planning and lay a foundation for assessing the impact of harm reduction efforts within this marginalized population.

Abstract Full-text [free] access

Young women’s perceptions of transactional sex and sexual agency: a qualitative study in the context of rural South Africa


Background: Evidence shows that HIV prevalence among young women in sub-Saharan Africa increases almost five-fold between ages 15 and 24, with almost a quarter of young women infected by their early-to-mid-20s. Transactional sex or material exchange for sex is a relationship dynamic that has been shown to have an association with HIV infection.

Methods: Using five focus group discussions and 19 in-depth interviews with young women enrolled in the HPTN 068 conditional cash transfer trial (2011-2015), this qualitative study explores young women’s perceptions of transactional sex within the structural and cultural context of rural South Africa. The analysis also considers the degree to which young women perceive themselves as active agents in such relationships and whether they recognise a link between transactional sex and HIV risk.

Results: Young women believe that securing their own financial resources will ultimately improve their bargaining position in their sexual relationships, and open doors to a more financially independent future. Findings suggest there is a nuanced relationship between sex, love and gifts: money has symbolic meaning, and money transfers, when framed as gifts, indicates a young woman’s value and commitment from the man. This illustrates the complexity of transactional sex; the way it is positioned in the HIV literature ignores that “exchanges” serve as fulcrums around which romantic relationships are organised. Finally, young women express agency in their choice of partner, but their agency weakens once they are in a relationship characterised by exchange, which may undermine their ability to translate perceived agency into STI and HIV risk reduction efforts.

Conclusions: This research underscores the need to recognise that transactional sex is embedded in adolescent romantic relationships, but that certain aspects make young women particularly vulnerable to HIV. This is especially true in situations of restricted choice and circumscribed employment opportunities. HIV prevention educational programmes could be coupled with income generation trainings, in order to leverage youth resilience and protective skills within the confines of difficult economic and social circumstances. This would provide
young women with the knowledge and means to more successfully navigate safer sexual relationships.

Abstract Full-text [free] access

4. Health systems and services

   Technology for tuberculosis, but why can’t we simply prevent it with proven tools that save lives?

Editor’s notes: Advances in diagnostic test technology have transformed the management of HIV and related infections. For HIV, we have seen the introduction of self-administered test kits as well as new approaches to HIV viral load testing and nucleic acid based infant diagnosis. Cryptococcal antigen screening can make prophylaxis and treatment more focused and potentially cost-effective. For tuberculosis the biggest revolution has been the widespread introduction of the geneXpert® system. The newest version, the Xpert® Ultra, is more sensitive than the original cartridge and is now being scaled up in countries including South Africa. Agizew and colleagues conducted a study in Botswana to compare how the Xpert® MTB/RIF cartridge performed when used in centralized or peripheral health facilities. Encouragingly there were few differences between the two levels, suggesting that the systems can be used close to the point of care. However, the authors did note a surprisingly high level of unsuccessful tests (15%) both at the central lab and at the peripheral clinic. Many of these test failures seem to have been because the sample was not processed correctly, and so should be amenable to better training for the health care workers performing the test. The yield of testing varied greatly between the 13 sites. Between 1% and 23% of samples were positive for tuberculosis, with an average of 14%. This may be because some sites were receiving specialized referrals. Of the 447 positive samples, 8% were shown to be rifampicin resistant. This figure is hard to interpret without more detail of the sample of patients in whom the test was performed. Resistance is always higher among those who have been treated previously and may be higher in those referred to specialized centres. Nonetheless, it demonstrates that there are a significant number of people with tuberculosis in Botswana who are very likely to have multi-drug resistant disease and need effective second line treatment. Technology comes with a price tag. In this study, the team bought test kits for $18 each, which makes it an expensive choice. However, if it leads to prompt treatment of multi-drug resistant disease and more accurate diagnosis of tuberculosis, including among those living with HIV, this might still be cost-effective.

A small implementation research study from a single provincial referral centre in Zambia also examined the use and results of geneXpert® screening. Masenga and colleagues found that 6.6% of 2374 samples tested by geneXpert® over the course of a year were positive for tuberculosis. An additional 1301 samples were tested by sputum microscopy. Their results suggest that geneXpert® was used mainly on people who were living with HIV, given that more than 90% of the positive samples came from people living with HIV. 5.9% of the 152 positive samples that were tested in the system were resistant to rifampicin, with no difference by gender. This study leaves many questions unanswered, such as the sampling strategy, the history of previous treatment and the outcomes of the diagnosis in terms of treatment regimen and success. However, it shines a light on the ways that new technology is now routine in some settings. We need more research from diverse settings to paint the full picture of implementation outside traditional research centres.
Zenner and colleagues revisit the question of the risks and benefits of treatment for latent tuberculosis infection. In a systematic review and network meta-analysis, they demonstrate once more that we have several effective ways to prevent tuberculosis among people living with HIV and that the harms are much smaller than the risks. The question remains why we have failed so badly to scale up preventive therapy for tuberculosis alongside the success in scale up of antiretrovirals.

Peripheral clinic versus centralized laboratory-based XPERT® MTB/RIF performance: experience gained from a pragmatic, stepped-wedge trial in Botswana


Background: In 2011, the Botswana National Tuberculosis Program adopted World Health Organization guidelines and introduced Xpert® MTB/RIF (Xpert®) assay to support intensified case finding among people living with HIV enrolling in care. An evaluation was designed to assess performance under operational conditions to inform the national Xpert® scale-up.

Methods: Xpert® was implemented from August 2012 through November 2014 with 13 GeneXpert® instruments (GeneXpert®) deployed in a phased approach over nine months: nine centralized laboratory and four point-of-care (POC) peripheral clinics. Clinicians and laboratorians were trained on the four-symptom tuberculosis screening algorithm and Xpert® testing. We documented our experience with staff training and GeneXpert® performance. Test results were extracted from GeneXpert® software; unsuccessful tests were analysed in relation to testing sites and trends over time.

Results: During 276 instrument-months of operation a total of 3630 tests were performed, of which 3102 (85%) were successful with interpretable results. Mycobacterium tuberculosis complex was detected for 447 (14%); of these, 36 (8%) were rifampicin resistant. Of all 3630 Xpert® tests, 528 (15%) were unsuccessful; of these 361 (68%) were classified as "error", 119 (23%) as "invalid" and 48 (9%) as "no result". The total number of recorded error codes was 385 and the most common reasons were related to sample processing (211; 55%) followed by power supply (77; 20%) and cartridge/module related (54; 14%). Cumulative incidence of unsuccessful test was similar between POC (17%, 95% CI: 11-25%) and centralized laboratory-based GeneXpert® instruments (14%, 95% CI: 11-17%; p = 0.140).

Conclusions: Xpert® introduction was successful in the Botswana setting. The incidence of unsuccessful test was similar by GeneXpert® location (POC vs. centralized laboratory). However, unsuccessful test incidence (15%) in our settings was higher than previously reported and was mostly related to improper sample processing. Ensuring adequate training among Xpert® testing staff is essential to minimize errors.

Abstract Full-text [free] access

Rifampicin resistance in mycobacterium tuberculosis patients using GeneXpert® at Livingstone Central Hospital for the year 2015: a cross sectional explorative study

Background: Since the recent introduction of GeneXpert® for the detection of Tuberculosis (TB) drug resistance mutations in both primary resistance and acquired resistance in Zambia, little has been documented in literature on the issue of rifampicin resistance especially in the face of a high National TB burden. The study aimed to determine the prevalence of rifampicin resistance in tuberculosis patients at Livingstone Central Hospital for the year 2015.

Methods: This was a cross sectional study conducted at Livingstone Central Hospital where we reviewed 152 records (from January 1, 2015 to 31st December 2015) involving patients who presented with clinically suspected TB or documented TB, whose samples were sent to the laboratory for GeneXpert® Mycobacterium tuberculosis/rifampicin testing. Statistical evaluations used a one-sample test of proportion and Fisher's exact test.

Results: The age of participants ranged from 8 months to 73 years old (median = 34). Of the participants with complete data on gender, 99 (66%) and 52 (34%) were males and females respectively. The TB co-infection with HIV prevalence was 98.3% (p < 0.001). Prevalence of rifampicin resistance was 5.9% and there was no statistical significant difference between being male or female (p = 0.721).

Conclusion: We were able to show from our study, evidence of rifampicin resistance at Livingstone Central Hospital. Hence, there was need for further in-depth research and appropriate interventions (i.e. close follow-up and patient care for drug resistance positive patients).

Abstract Full-text [free] access

Treatment of latent tuberculosis infection: an updated network meta-analysis


Background: Treatment of latent tuberculosis infection (LTBI) is an important component of tuberculosis (TB) control, and this study updates a previous network meta-analysis of the best LTBI treatment options to inform public health action and programmatic management of LTBI.

Purpose: To evaluate the comparative efficacy and harms of LTBI treatment regimens aimed at preventing active TB among adults and children.

Data sources: PubMed, Embase, and Web of Science from indexing to 8 May 2017; clinical trial registries; and conference abstracts. No language restrictions were applied.

Study selection: Randomized controlled trials that evaluated human LTBI treatments and recorded at least 1 of 2 prespecified end points (hepatotoxicity and prevention of active TB).

Data extraction: 2 investigators independently extracted data from eligible studies and assessed study quality according to a standard protocol.

Data synthesis: The network meta-analysis of 8 new and 53 previously included studies showed that isoniazid regimens of 6 months (odds ratio [OR], 0.65 [95% credible interval (CrI), 0.50 to 0.83]) or 12 to 72 months (OR, 0.50 [CrI, 0.41 to 0.62]), rifampicin-only regimens (OR, 0.41 [CrI, 0.19 to 0.85]), rifampicin-isoniazid regimens of 3 to 4 months (OR, 0.53 [CrI, 0.36 to 0.78]), rifampicin-isoniazid-pyrazinamide regimens (OR, 0.35 [CrI, 0.19 to 0.61]), and rifampicin-pyrazinamide regimens (OR, 0.53 [CrI, 0.33 to 0.84]) were efficacious compared with placebo. Evidence existed for efficacy of weekly rifapentine-isoniazid regimens compared with no
treatment (OR, 0.36 [CrI, 0.18 to 0.73]). **No conclusive evidence showed that HIV status altered treatment efficacy.**

Limitation: Evidence was sparse for many comparisons and hepatotoxicity outcomes, and risk of bias was high or unknown for many studies.

Conclusion: **Evidence exists for the efficacy and safety of 6-month isoniazid monotherapy, rifampicin monotherapy, and combination therapies with 3 to 4 months of isoniazid and rifampicin.**

Abstract Full-text [free] access

**Cryptoccal meningitis – the unacceptable consequence of leaving people behind during ART scale up**

*Editor's notes:* Cryptoccal meningitis is a severe disease that occurs in people with advanced immune suppression. Its occurrence is an indicator that an HIV treatment programme is not working well, as it is rare in people whose CD4 count is above 100 cells per microlitre. Rajasingham and colleagues have tried to estimate the current burden of disease. This is not straightforward, as the number and proportion of people with advanced HIV disease is changing with the increasing scale up of antiretroviral therapy and earlier HIV diagnosis. Nonetheless, severe immune suppression still occurs in those whose HIV infection remains undiagnosed or is diagnosed too late; among those who are not started on effective ARVs promptly and among those in whom ART fails and who are not managed effectively by the ART treatment programme. The authors estimate that there could be more than 180 000 deaths from cryptoccal meningitis with the large majority (136 000) in Africa. This makes Cryptococcus responsible for more than 15% of HIV-related deaths, second only to tuberculosis as a documented cause. The authors emphasize the need for earlier diagnosis of HIV and better linkage to quality care programmes. In the meantime, there are also advances in the screening, prophylaxis and treatment of Cryptococcus itself, which require investment in laboratory services and affordable medicines that can save lives until the effects of good ART improves the immune status.

Cassim and colleagues have developed a novel approach to costing different approaches to the roll out of technology for screening for cryptoccal antigen in the blood of people with advanced HIV infection. Depending on the numbers of samples to be tested in the laboratory, a mix of single use lateral flow assays and automated enzyme immunoassays makes most sense. The aim is to allow the more cost-effective high-volume sites to subsidize the low volume sites in order to ensure that as many people living with advanced HIV infection as possible can be screened.

**Global burden of disease of HIV-associated cryptoccal meningitis: an updated analysis**


Background: **Cryptococcus is the most common cause of meningitis in adults living with HIV in sub-Saharan Africa.** Global burden estimates are crucial to guide prevention strategies and to determine treatment needs, and we aimed to provide an updated estimate of global incidence of HIV-associated cryptoccal disease.
Methods: We used 2014 Joint UN Programme on HIV and AIDS estimates of adults (aged >15 years) with HIV and antiretroviral therapy (ART) coverage. Estimates of CD4 less than 100 cells per μL, virological failure incidence, and loss to follow-up were from published multinational cohorts in low-income and middle-income countries. We calculated those at risk for cryptococcal infection, specifically those with CD4 less than 100 cells/μL not on ART, and those with CD4 less than 100 cells per μL on ART but lost to follow-up or with virological failure. Cryptococcal antigenaemia prevalence by country was derived from 46 studies globally. Based on cryptococcal antigenaemia prevalence in each country and region, we estimated the annual numbers of people who are developing and dying from cryptococcal meningitis.

Findings: We estimated an average global cryptococcal antigenaemia prevalence of 6.0% (95% CI 5.8-6.2) among people with a CD4 cell count of less than 100 cells per μL, with 278,000 (95% CI 195,500-340,600) people positive for cryptococcal antigen globally and 223,100 (95% CI 150,600-283,400) incident cases of cryptococcal meningitis globally in 2014. Sub-Saharan Africa accounted for 73% of the estimated cryptococcal meningitis cases in 2014 (162,500 cases [95% CI 113,600-193,900]). Annual global deaths from cryptococcal meningitis were estimated at 181,100 (95% CI 119,400-234,300), with 135,900 (75%; [95% CI 93,900-163,900]) deaths in sub-Saharan Africa. Globally, cryptococcal meningitis was responsible for 15% of AIDS-related deaths (95% CI 10-19).

Interpretation: Our analysis highlights the substantial ongoing burden of HIV-associated cryptococcal disease, primarily in sub-Saharan Africa. Cryptococcal meningitis is a metric of HIV treatment programme failure; timely HIV testing and rapid linkage to care remain an urgent priority.

Abstract access

Estimating the cost-per-result of a national reflexed cryptococcal antigenaemia screening program: Forecasting the impact of potential HIV guideline changes and treatment goals


Introduction: During 2016, the National Health Laboratory Service (NHLS) introduced laboratory-based reflexed Cryptococcal antigen (CrAg) screening to detect early Cryptococcal disease in immunosuppressed HIV+ patients with a confirmed CD4 count of 100 cells/μL or less.

Objective: The aim of this study was to assess cost-per-result of a national screening program across different tiers of laboratory service, with variable daily CrAg test volumes. The impact of potential ART treatment guideline and treatment target changes on CrAg volumes, platform choice and laboratory workflow are considered.

Methods: CD4 data (with counts ≤ 100 cells/μL) from the fiscal year 2015/16 were extracted from the NHLS Corporate Date Warehouse and used to project anticipated daily CrAg testing volumes with appropriately-matched CrAg testing platforms allocated at each of 52 NHLS CD4 laboratories. A cost-per-result was calculated for four scenarios, including the existing service status quo (Scenario-I), and three other settings (as Scenarios II-IV) which were based on information from recent antiretroviral (ART) guidelines, District Health Information System (DHIS) data and UNAIDS 90/90/90 HIV/AIDS treatment targets. Scenario-II forecast CD4 testing offered only to new ART initiates recorded at DHIS. Scenario-III projected all patients notified...
as HIV+, but not yet on ART (recorded at DHIS) and Scenario-IV forecast CrAg screening in 90% of estimated HIV+ patients across South Africa (also DHIS). Stata was used to assess daily CrAg volumes at the 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles across 52 CD4-laboratories. Daily volumes were used to determine technical effort/ operator staff costs (% full time equivalent) and cost-per-result for all scenarios.

Results: Daily volumes ranged between 3 and 64 samples for Scenario-I at the 5th and 95th percentile. Similarly, daily volumes ranges of 1-12, 2-45 and 5-100 CrAg-directed samples were noted for Scenario’s II, III and IV respectively. A cut-off of 30 CrAg tests per day defined use of either LFA or EIA platform. LFA cost-per-result ranged from $8.24 to $5.44 and EIA cost-per-result between $5.58 and $4.88 across the range of test volumes. The technical effort across scenarios ranged from 3.2-27.6% depending on test volumes and platform used.

Conclusion: The study reported the impact of programmatic testing requirements on varying CrAg test volumes that subsequently influenced choice of testing platform, laboratory workflow and cost-per-result. A novel percentiles approach is described that enables an overview of the cost-per-result across a national program. This approach facilitates cross-subsidisation of more expensive lower volume sites with cost-efficient, more centralized higher volume laboratories, mitigating against the risk of costing tests at a single site.