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HIV this month. Issue no. 10. November 2017

Welcome to the 10th issue of **HIV this month!** In this issue, we cover the following topics:

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HIV this month, published by UNAIDS, is a selective scan of new HIV-related information found in scientific journals. The Editors of HIV this month interpret original abstracts and provide editorial comment, so that information may be easily understood by people responding to the HIV epidemic in many diverse settings. The selection of material, its abridgement and other editorial changes, and also the original editorial comment are the responsibility of the Editors and do not represent any official statement of UNAIDS. It should be noted that (except for open access journals, e.g. PLoS) the authors and/or publishers retain copyright in the original published material to which HIV this month refers.

1. HIV testing and treatment

Improving access to HIV testing—still the most important step to improve the lives of people living with HIV?

Editor's notes: *The target for HIV testing is very clear and well understood as the first 90 in the UNAIDS treatment targets. However, estimating the proportion of people living with HIV who know their status is not completely straightforward. UNAIDS uses various data sources and a well described algorithm to make its annual estimates. For some countries, population based surveys allow a random sample of the population to be interviewed and tested for HIV. Nonetheless, such surveys only occur periodically and so data may be out of date. People who were HIV-negative a few years ago may now be HIV positive and people who know that they were tested a few years ago and think that they know their status may in fact have acquired HIV in the meantime. Staveteig and colleagues have used the most recent demographic and health surveys from 16 countries in sub-Saharan Africa to estimate the first 90 and to analyse the demographic characteristics associated with knowing one's HIV status. The authors discuss some of the challenges in the assumptions needed for this estimation process. However, the surveys had excellent participation and a high rate of acceptance of HIV testing, so that out of more than 14 000 people living with HIV across the countries, the authors are able to state that 54% know their status. The proportion in different countries ranges from 26% in Sierra Leone to 84% in Rwanda. Their analysis does not present very surprising associations. We have come to expect that men, young people and those with less than primary education are found to be less likely to know their status. However, the study provides a direct estimate from survey data and as such helps to triangulate with other estimates from the region.*

In general, the West and Central African region lags behind the East and Southern African region when it comes to access to HIV testing, linkage to treatment and viral suppression. A catch-up plan has been developed and endorsed at high level political meetings in most countries in the region. The study by Inghels and colleagues from Côte d'Ivoire is therefore important. They demonstrate that among 273 people recently diagnosed with HIV at the blood donors' centre, almost half could have been diagnosed up to five years earlier if health care staff had followed guidelines to propose testing for indicator clinical conditions such as extreme weight loss, repeated fevers or shingles. Approximately a quarter of people recently diagnosed with HIV had recognized risk factors for HIV (apart from their clinical presentation), but only approximately one-sixth, a small minority, of people had mentioned it to their healthcare professional. If we are to catch up and ensure that 90% of people living with HIV have known their status by 2020, we need to maximize efforts to use a full range of differentiated HIV testing approaches. Health care staff must offer HIV tests routinely to people with clinical indicator conditions. Staff at all levels of the health system must also promote an environment in which people with risk behaviours for HIV infection feel comfortable to be able to raise it and discuss it.

Reaching the 'first 90': gaps in coverage of HIV testing among people living with HIV in 16 African countries.

Staveteig S, Croft TN, Kampa KT, Head SK. PLoS One. 2017 Oct 12;12(10):e0186316. doi: 10.1371/journal.pone.0186316. eCollection 2017.

Background: UNAIDS has recently proposed a set of three ambitious targets that, if achieved, are predicted to end the AIDS epidemic by 2030. **The targets**, known as **90-90-90**, call for 90% of people living with HIV (PLHIV) to know their status, 90% of PLHIV to receive antiretroviral therapy, and 90% of those on antiretroviral therapy to achieve viral suppression by the year 2020. We **examine the first**

of these targets, focusing on sub-Saharan Africa, the region of the world most affected by HIV, to measure the proportion of PLHIV estimated to know their HIV status, and to identify background and behavioral characteristics significantly associated with gaps in ever testing among PLHIV.

Methods and Findings: We analyze cross-sectional population-based data from the Demographic and Health Surveys (DHS) and AIDS Indicator Surveys (AIS) fielded since 2010 in 16 sub-Saharan African countries where voluntary serological testing was recently conducted: Burkina Faso, Cameroon, Chad, Cote d'Ivoire, Ethiopia, Gabon, Lesotho, Malawi, Namibia, Rwanda, Sierra Leone, Tanzania, Togo, Uganda, Zambia, and Zimbabwe. Survey response rates averaged 95.0% (range 89.3-99.5%), while consent to serotesting averaged 94.9% (range 88.7-99.6%). **This study, which includes more than 14 000 respondents living with HIV, finds that 69% of PLHIV in the average study country have ever been tested for HIV (range 34-95%).** Based on timing of the last test and on ART coverage, **we estimate that 54% of PLHIV in the average country are aware of their status (range 26-84%).** **Adjusted logistic regression finds that men (median adjusted odds ratio [AOR] = 0.38), adults with less than primary education (median AOR = 0.31), and adolescents (median AOR = 0.32) are consistently less likely to have ever been tested for HIV than women, adults with secondary and above education, and adults age 30-39, respectively.** In most countries unadjusted logistic regression also finds significant gaps in testing among the poorest groups and those reporting never having had sex.

Conclusion: The fact that **an average of 54% of PLHIV in these 16 countries are estimated to know their status reflects encouraging progress.** However, **not only is this average far short of the 90% target set by UNAIDS for 2020, but it also implies that in the average study country nearly one-half of PLHIV are unable to access lifesaving care and treatment because they are unaware that they are HIV-positive.** **Several gaps in HIV testing coverage exist,** particularly among adolescents, the least educated, and men. While the need to target demographic groups at greatest risk of HIV continues, additional interventions focused on reaching men and on reaching socially vulnerable populations such as adolescents, the poorest, and the least educated are essential.

[Abstract](#) [Full-text \[free\] access](#)

Missed opportunities for HIV testing among newly diagnosed HIV-infected adults in Abidjan, Côte d'Ivoire.

Inghels M, Niangoran S, Minga A, Yoboue JM, Dohoun L, Yao A, Eholié S, Anglaret X, Danel C. PLoS One. 2017 Oct 4;12(10):e0185117. doi: 10.1371/journal.pone.0185117. eCollection 2017

Background: HIV testing is crucial for starting ART earlier in HIV-infected people. **We describe Missed Opportunities (MO) for HIV testing among adults newly diagnosed with HIV in Abidjan, Côte d'Ivoire.**

Methods: Between April 2nd 2013 and April 1st 2014, a cross-sectional study was conducted among all adults newly diagnosed (< 1year) for HIV at the Blood Donors Medical Center of Abidjan with face to face questionnaire. An MO for HIV testing was defined as a medical consultation for a clinical indicator (e.g. symptoms, hospitalization, and pregnancy) or a non-clinical indicator (e.g. high-risk sexual behavior, HIV-infected partner) potentially related to an HIV infection but did not lead to HIV test proposal by a health care professional.

Results: Of the 341 patients who attended the center during this period, 273 (157 women and 116 men) were included in this analysis. 130 (47.6%) reported at least one medical consultation for

an indicator relevant for a test proposal between 1 month and five years prior to their diagnosis. Among them, 92 (77.3%) experienced at least one MO for testing. **The 273 included patients reported a total of 216 indicators; 146 (67.6%) were reported without test proposal and thus were MO. Hospitalization, extreme loss of weight, chronic or repeat fever and herpes zoster were the indicators with the largest number of MO. While 66 (24.2%) patients experienced non-clinical indicators relevant to risk of HIV infection, only 11 (4.0%) mentioned it to a health professional.**

Conclusion: **MO for HIV testing are frequent, even in situations for which testing is clearly recommended.** Better train healthcare professionals and creating new opportunities of testing inside and, outside of medical settings are crucial to improve HIV control.

[Abstract](#) [Full-text \[free\] access](#)

Despite better access to HIV treatment we need stronger evidence based guidance on treating people with serious complications of advanced HIV infection

Editor's notes: *The emphasis for scaling up HIV treatment usually focuses on outpatient and primary care clinics with increasing decentralization to the community. It is therefore sobering to see the results of a randomized trial conducted at a national referral hospital in Zambia. Andrews and colleagues report on 209 adults admitted to hospital with sepsis and hypotension, a combination referred to as septic shock. Several important points emerge. Almost 90% of patients admitted with this serious condition were HIV-positive. Most had only been diagnosed with HIV infection in the last three months, and approximately half were taking ART. The median CD4 count was only 70 cells per microlitre. Almost half had a history of having tuberculosis and one quarter were currently on anti-tuberculosis treatment at the time of admission to hospital. Most were also anaemic, with an average haemoglobin of 7.8 g/dl. Mortality from septic shock has been falling in Europe and the United States of America largely due to more intensive management of intravenous fluids and blood pressure. The focus has been on strict protocols to ensure that all patients get the best treatment. However, there has been debate about the best approach to take when less sophisticated monitoring and supportive technology such as artificial ventilation is not available. In this Zambian tertiary hospital setting, only one patient was able to be managed in the intensive care unit due to resource constraints. Patients were randomized to receive a protocolized intensive fluid and blood pressure resuscitation or to receive the more standard care with the responsible physicians making the decisions. The death rate from this severe condition was very high. 85 of the 209 patients randomized died. However, despite receiving more intravenous fluids, more blood transfusions and more drugs to raise blood pressure, the outcomes were worse in the group treated according to the protocol with 48% mortality compared to 33% in the standard care arm. As always, the lesson is that many of these deaths could have been avoided if we were able to diagnose, link and treat people living with HIV much earlier in the course of their infection. However, there is also an important caution that treatments that make good sense and seem the best course of action may in fact make the situation worse, even if the same treatments have been shown in other contexts to be beneficial. Such information will only come from randomized trials, and the authors should be congratulated for being bold enough to conduct a high-quality study that should make us reflect on our preconceptions about how best to treat seriously ill patients in resource poor settings.*

Andrade and colleagues have reviewed the literature in order to determine the best approach to treating critically unwell people living with HIV who are admitted to intensive care units. They examined whether starting ARVs while the person was already critically ill was associated with better outcomes. Patients in intensive care may already have many different medicines, as well as altered

metabolism. In addition, ARVs can provoke immune reconstitution inflammatory syndromes that have been shown to make outcomes worse in some serious conditions such as cryptococcal meningitis. On the other hand, the evidence from patients with tuberculosis is clear – starting ARVs as soon as possible is associated with better outcomes. In this review and meta-analysis, there was a clear short-term advantage to starting ARVs while the patient was still in intensive care. The data were not sufficient to tell whether the longer-term outcome was also improved by the earlier start of ART. One limitation is that all the studies reviewed were observational, and the decision to start ARVs was not randomized, so that it is plausible that clinicians may have started ARVs more willingly in those patients who were most likely to survive. Nonetheless, in the absence of randomized trials, this study makes a strong case for starting ARVs promptly even in the sickest patients.

Effect of an early resuscitation protocol on in-hospital mortality among adults with sepsis and hypotension: a randomized clinical trial.

Andrews B, Semler MW, Muchemwa L, Kelly P, Lakhi S, Heimbürger DC, Mabula C, Bwalya M, Bernard GR. *JAMA*. 2017 Oct 3;318(13):1233-1240. doi: 10.1001/jama.2017.10913.

Importance: The effect of an early resuscitation protocol on sepsis outcomes in developing countries remains unknown.

Objective: **To determine whether an early resuscitation protocol with administration of intravenous fluids, vasopressors, and blood transfusion decreases mortality among Zambian adults with sepsis and hypotension compared with usual care.**

Design, setting, and participants: **Randomized clinical trial of 212 adults with sepsis** (suspected infection plus ≥ 2 systemic inflammatory response syndrome criteria) **and hypotension** (systolic blood pressure ≤ 90 mm Hg or mean arterial pressure ≤ 65 mm Hg) **presenting to the emergency department at a 1500-bed referral hospital in Zambia between October 22, 2012, and November 11, 2013. Data collection concluded December 9, 2013.**

Interventions: **Patients were randomized 1:1 to either (1) an early resuscitation protocol for sepsis** (n = 107) that included intravenous fluid bolus administration with monitoring of jugular venous pressure, respiratory rate, and arterial oxygen saturation and treatment with vasopressors targeting mean arterial pressure (≥ 65 mm Hg) and blood transfusion (for patients with a hemoglobin level < 7 g/dL) **or (2) usual care** (n = 105) in which treating clinicians determined hemodynamic management.

Main outcomes and measures: **The primary outcome was in-hospital mortality and the secondary outcomes included the volume of intravenous fluid received and receipt of vasopressors.**

Results: **Among 212 patients randomized to receive either the sepsis protocol or usual care, 3 were ineligible and the remaining 209 completed the study and were included in the analysis** (mean [SD] age, 36.7 [12.4] years; 117 men [56.0%]; 187 [89.5%] positive for the human immunodeficiency virus). **The primary outcome of in-hospital mortality occurred in 51 of 106 patients (48.1%) in the sepsis protocol group compared with 34 of 103 patients (33.0%) in the usual care group** (between-group difference, 15.1% [95% CI, 2.0%-28.3%]; relative risk, 1.46 [95% CI, 1.04-2.05]; P = .03). **In the 6 hours after presentation to the emergency department, patients in the sepsis protocol group received a median of 3.5 L** (interquartile range, 2.7-4.0 L) **of intravenous fluid compared with 2.0 L** (interquartile range, 1.0-2.5 L) **in the usual care group** (mean difference, 1.2 L [95% CI, 1.0-1.5 L]; P < .001). **Fifteen patients (14.2%) in the sepsis protocol group and 2 patients (1.9%) in the usual care group received vasopressors** (between-group difference, 12.3% [95% CI, 5.1%-19.4%]; P < .001).

Conclusions and relevance: **Among adults with sepsis and hypotension, most of whom were positive for HIV, in a resource-limited setting, a protocol for early resuscitation with administration of intravenous fluids and vasopressors increased in-hospital mortality compared with usual care.** Further studies are needed to understand the effects of administration of intravenous fluid boluses and vasopressors in patients with sepsis across different low- and middle-income clinical settings and patient populations.

[Abstract access](#)

Highly active antiretroviral therapy for critically ill HIV patients: a systematic review and meta-analysis.

Andrade HB, Shinotsuka CR, da Silva IRF, Donini CS, Yeh Li H, de Carvalho FB, Americano do Brasil PEA, Bozza FA, Miguel Japiassu A. PLoS One. 2017 Oct 24;12(10):e0186968. doi:10.1371/journal.pone.0186968. eCollection 2017

Introduction: It is unclear whether the treatment of an HIV infection with highly active antiretroviral therapy (HAART) affects intensive care unit (ICU) outcomes. In this paper, **we report the results of a systematic review and meta-analysis performed to summarize the effects of HAART on the prognosis of critically ill HIV positive patients.**

Materials and methods: **A bibliographic search was performed in 3 databases (PubMed, Web of Science and Scopus) to identify articles that investigated the use of HAART during ICU admissions for short- and long-term mortality or survival.** Eligible articles were selected in a staged process and were independently assessed by two investigators. **The methodological quality of the selected articles was evaluated using the Methodological Index for Non-Randomized Studies (MINORS) tool.**

Results: **Twelve articles met the systematic review inclusion criteria and examined short-term mortality. Six of them also examined long-term mortality (≥90 days) after ICU discharge. The short-term mortality meta-analysis showed a significant beneficial effect of initiating or maintaining HAART during the ICU stay (random effects odds ratio 0.53, p = 0.02). The data analysis of long-term outcomes also suggested a reduced mortality when HAART was used, but the effect of HAART on long-term mortality of HIV positive critically ill patients remains uncertain.**

Conclusions: **This meta-analysis suggests improved survival rates for HIV positive patients who were treated with HAART during their ICU admission.**

[Abstract](#) [Full-text \[free\] access](#)

The third 90—ensuring adherence to ART needs approaches tailored to the clinical and social context of individuals

Editor's notes: *The third 90, ensuring that people who are on antiretroviral therapy are supported to adhere well enough to suppress their viral load, is key to preventing drug resistance and to ensuring efficiency of resources as treatment is scaled up to all people living with HIV. Previous studies have demonstrated how useful SMS reminders can be for many people taking ARV medicines, and this evidence is now incorporated into WHO guidance on ART. However, a randomized trial by Linnemayr and colleagues among adolescents and young adults in Kampala, Uganda found no benefit after one year of either a weekly reminder or a weekly reminder with the option to respond. There are no magic bullets to ensure adherence. SMS reminders may well suit some individuals,*

whereas others will need different approaches. The differentiated care approach to ART emphasizes the need to develop the best treatment and support service for each individual, according to their specific social context and clinical situation.

Text messaging for improving antiretroviral therapy adherence: no effects after 1 year in a randomized controlled trial among adolescents and young adults.

Linnemayr S, Huang H, Luoto J, Kambugu A, Thirumurthy H, Haberer JE, Wagner G, Mukasa B. Am J Public Health. 2017 Dec;107(12):1944-1950. doi:10.2105/AJPH.2017.304089. Epub 2017 Oct 19.

Objectives: To assess the effectiveness of Short Message Service (SMS) reminder messages on antiretroviral and cotrimoxazole prophylaxis adherence among HIV-positive youths as well as the relative effectiveness of SMS with and without a response option.

Methods: Eligible HIV-positive patients aged 15 to 22 years at 2 HIV clinics in Kampala, Uganda, participated in a year-long parallel individual-randomized controlled trial and were assigned in a 1-to-1-to-1 ratio to a weekly SMS message group, weekly SMS message with response option group, or a usual-care control group.

Results: We enrolled 332 participants. Electronically measured mean adherence was 67% in the control group, 64% in the 1-way SMS group (95% confidence interval [CI] = 0.77, 1.14), and 61% in the 2-way SMS group (95% CI = 0.75, 1.12) in an intent-to-treat analysis. Results for secondary outcomes and complete-case analysis were similarly statistically insignificant across groups.

Conclusions: Despite previous evidence that interventions using SMS reminders can promote antiretroviral therapy adherence, this study shows that they are not always effective in achieving behavior change. More research is needed to find out for whom, and under what conditions, they can be beneficial.

[Abstract access](#)

2. Combination prevention

Women at substantial risk of HIV infection can and should take PrEP

Editor's notes: *PrEP is now generally accepted to be one of the major reasons that the number of new infections among gay men and other men who have sex with men is falling in urban centres in Europe and the USA. The PROUD and Ipergay randomized trials demonstrated efficacy of over 85%. This proved conclusively that among men who were motivated to take tablets either every day or around the time of sex, PrEP could be highly effective. The data for vaginal rather than anal sex is less straightforward. The Partners PrEP trial and Demonstration project also showed high efficacy among both men and women in serodiscordant couples. However, several studies among women at high risk of acquiring HIV showed no effect overall, because women were not taking the tablets for a variety of reasons. Pharmacokinetic studies show that tenofovir-emtricitabine (the most widely used and recommended medicines for PrEP) reaches considerably higher levels in the rectal tissues than in the vagina. As a result, we know that PrEP adherence is vital to achieve protective levels for vaginal sex, and daily dosage rather than an 'on demand' regimen is still recommended. The ADAPT trial in Cape Town has now published its final results. In this trial, young South African women were given daily PrEP in a controlled setting for four weeks before being randomized to three different regimens. One group took PrEP every day, one group took PrEP before and after sex and the third*

group took two tablets each week with an additional dose after sex. Adherence was measured using an electronic device that recorded when the pills were accessed, as well as self-report. Drug levels were also measured. Although this is a somewhat artificial situation involving only 59 or 60 women in each group, the results are important and confirm that for women, only daily PrEP should be recommended. The trial also shows that women were able to adhere well, with 75% adherence and 75% of sex acts covered by PrEP among women taking the medicines every day during the follow-up period. Neither of the other two regimens provided adequate coverage and all four incident infections occurred in these two groups (although the numbers are too small to draw reliable conclusions about the efficacy).

Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial.

Bekker LG, Roux S, Sebastien E, Yola N, Amico KR, Hughes JP, Marzinke MA, Hendrix CW, Anderson PL, Elharrar V, Stirratt M, Rooney JF, Piwowar-Manning E, Eshleman SH, McKinstry L, Li M, Dye BJ, Grant RM; HPTN 067 (ADAPT) study team. *Lancet HIV*. 2017 Oct 3. pii: S2352-3018(17)30156-X. doi: 10.1016/S2352-3018(17)30156-X.

Background: The relative feasibility and acceptability of daily versus non-daily dosing of oral HIV pre-exposure prophylaxis (PrEP) among women are unknown. **We aimed to investigate the feasibility of non-daily PrEP regimens in adult women.**

Methods: **We did a randomised, open-label, phase 2 clinical trial (HPTN 067/ADAPT) of oral PrEP with emtricitabine plus tenofovir disoproxil fumarate at a research centre in Cape Town, South Africa. Participants were adult women (age ≥18 years) who received directly observed dosing once a week for 5 weeks followed by random assignment (1:1:1) at week 6 to one of three unblinded PrEP regimens for self-administered dosing over 24 weeks: daily; time-driven (twice a week plus a post-sex dose); or event-driven (one tablet both before and after sex). Primary outcomes were PrEP coverage (at least one dose within the 4 days before sex and one dose within 24 h after sex), pills needed or used to achieve regimen-specific adherence and coverage, and symptoms and side-effects.** All analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01327651; the trial is completed, and this report presents the final analysis.

Findings: **Between Sept 12, 2011, and Oct 3, 2012, 191 women were enrolled to the trial. 178 (93%) completed directly observed dosing and were randomly assigned one of the three PrEP regimens for the self-administered phase: 59 were allocated the daily regimen, 59 the time-driven regimen, and 60 the event-driven regimen. Median age of women was 26 years (IQR 21-37; range 18-52). In women allocated the daily regimen, 1459 (75%) of 1952 sex events were covered by PrEP, compared with 599 (56%) of 1074 sex events among those assigned the time-driven regimen (odds ratio [OR] 2.35, 95% CI 1.43-3.83; p=0.0007) and 798 (52%) of 1542 sex events among those allotted the event-driven regimen (2.76, 1.68-4.53; p<0.0001). Fewer pills were needed for complete adherence in women allocated non-daily regimens (vs daily regimen, relative mean 2.53 [95% CI 2.39-2.69] for the time-driven regimen and 4.16 [3.59-4.82] for the event-driven regimen; p<0.0001). Side-effects were uncommon. Eight HIV seroconversions occurred overall, with four documented during the self-administered phase (two with the time-driven regimen and two with the event-driven regimen). Adherence to the assigned regimen was 75% (7283 of 9652 doses taken) for women allocated the daily regimen compared with 65% for those assigned the time-driven regimen (2367 of 3616 doses taken; p=0.0028) and 53% for those allotted the event-driven regimen (1161 of 2203 doses taken; p<0.0001). When sex was reported in the previous**

week, PrEP drugs were detected (above the lower limits of quantification) **more frequently in women assigned the daily regimen** (73 [68%] of 107 samples) **than in those allocated the time-driven regimen** (42 [58%] of 72 samples) **and the event-driven regimen** (41 [41%] of 99 samples).

Interpretation: **Daily PrEP dosing resulted in higher coverage of sex events, increased adherence to the regimen, and augmented drug concentrations than did either time-driven or event-driven dosing.** These findings support recommendations for daily use of PrEP with oral emtricitabine plus tenofovir disoproxil fumarate in women.

[Abstract access](#)

Health economics of PrEP in Europe

Editor's notes: *One of the most common questions for policy makers considering the introduction of PrEP is how much it will cost and whether the benefits will outweigh the costs. The answers to these questions will be dependent on the specific context but will be strongly influenced by four factors: the cost of PrEP (including its delivery); the savings due to reduced costs of HIV care; the effectiveness of PrEP; and the incidence of HIV in the population who receive PrEP. The effectiveness and the incidence can be combined to calculate the number needed to treat to prevent an HIV infection. As mentioned above, both PROUD and Ipergay demonstrated excellent effectiveness in populations that were highly at risk, as shown by the very high incidence in the placebo or deferred arms of these studies. Durand-Zaleski and colleagues present their analysis of the costs and benefits of PrEP as used in the Ipergay study. Most participants were in France, where lifetime costs of HIV treatment are estimated to be more than 500 000 euros. At the time of Ipergay, the medicines for PrEP cost more than 500 euros monthly, but subsequently generic medicines have become available in France for around 180 euros monthly, and the price in France is approximately US\$60 per month from Indian suppliers over the internet. When other health related costs are included, the costs to prevent an HIV infection vary from 27 000 to 75 000 euros depending on the costs of the medicines. The confidence intervals around these estimates are wide because the trial was stopped before there were too many infections given the clear evidence of efficacy. This model does not discount future costs, as it uses a short time horizon. The model also does not consider ongoing transmission, which the authors estimate to be around two to three additional people given data from Ipergay's sexual mixing data. So, the conclusions that the benefits of PrEP outweigh the costs are based on conservative assumptions for this population. However, it is important to recognize that the study population had an HIV incidence of 6.6 per 100 person-years and the incidence was more than nine per 100 person-years in the participants recruited into the placebo arm in the two Paris sites. This led to an estimated number needed to treat of around 18 overall and around 13 for the Parisian sites. WHO recommends that PrEP is offered to all people at significant risk of HIV infection, in whom the incidence might be more than three per 100 person-years. An incidence of 3% would more than double the costs per infection averted calculated in this study, and an incidence of 0.66% (which would still represent an important and ongoing HIV epidemic, such as that seen on average in recent PHIA studies in Zambia and twice that seen in Malawi) would increase the costs per infection averted by tenfold. From a health economic perspective, PrEP should always be prioritized to people who are most at risk. From a human rights perspective, PrEP should be offered to anyone who wants it and in whom the epidemiological and psychological benefits outweigh the very small clinical risks of taking tenofovir and emtricitabine.*

Cambiano and colleagues have modelled the potential impact and costs of PrEP in the UK population of gay men and men who have sex with men. They assumed that PrEP would be offered to HIV-negative men who reported condomless anal sex in the past three months. Over the next 80 years,

HIV infections would be prevented both directly and because of ongoing transmission to other men, leading to considerable cost-savings in terms of health care costs. Overall, the authors predict that such a PrEP programme might save one billion pounds and avert approximately 25% of the HIV infections that would have been seen in the absence of the programme. The results included a wide range of probabilistic uncertainty sampling. The largest changes to their estimates would come from reductions in the costs of ARVs (for both treatment and for PrEP). If PrEP was considerably cheaper, the time to break even in costs terms would be shorter. On the one hand, we need models with a long-time horizon to capture all the benefits of preventing HIV infection today. On the other hand, changes in technologies that may arise in the future cannot be incorporated into such models despite our hope that HIV prevention and treatment is likely to be very different over the next decades.

Costs and benefits of on-demand HIV pre-exposure prophylaxis in MSM.

Durand-Zaleski I, Mutuon P, Charreau I, Tremblay C, Rojas D, Pialoux G, Chidiac C, Capitant C, Spire B, Cotte L, Chas J, Meyer L; Molina JM for the ANRS IPERGAY study group. AIDS. 32(1):95–102, 2018 Jan 2. doi:10.1097/QAD.0000000000001658. [Epub 2017 Oct 12]

Objectives: We undertook the economic evaluation of the double-blind randomized ANRS-IPERGAY trial, which showed the efficacy of on-demand preexposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF)-emtricitabine (FTC) in preventing HIV infection among high-risk MSM.

Design and methods: The economic evaluation was prospective. Counseling, drugs (TDF-FTC at €500.88 for 30 tablets), tests, visits, and hospital admissions were valued based on in-trial use. The cost of on-demand PrEP/HIV infection averted was compared with the yearly and lifetime costs of HIV infection in France in a cost and benefits analysis.

Results: The yearly number of participants needed to treat to prevent one HIV infection was 17.6 (95% confidence interval=10.7–49.9). The annual cost of counseling was €690/participant. The total 1-year costs of PrEP were €4271/participant, of which €3129 (73%) were drug costs corresponding to 15 tablets of TDF-FTC/month. The yearly cost of on-demand PrEP to avoid one infection was €75 258. Using TDF-FTC generic (€179.9/30 tablets) reduced the 1-year costs of on-demand PrEP to €2271/participant and €39 970/infection averted, respectively. Using TDF-FTC at international market discounted prices (€60/30 tablets) reduced the costs to €1517/participant and the cost to €26 787/infection averted, comparable with the yearly treatment cost of HIV infection in France. On-demand PrEP was found to be cost saving in France if the duration of exposure was less than 7.5 years at current drug price and 13 years at generic price.

Conclusion: *On-demand PrEP in high-risk MSM with TDF-FTC can be considered cost saving.* Other benefits include the treatments of other diseases and reductions in secondary infections.

[Abstract access](#)

Cost-effectiveness of pre-exposure prophylaxis for HIV prevention in men who have sex with men in the UK: a modelling study and health economic evaluation.

Cambiano V, Miners A, Dunn D, McCormack S, Ong KJ, Gill ON, Nardone A, Desai M, Field N, Hart G, Delpech V, Cairns G, Rodger A, Phillips AN. Lancet Infect Dis. 2017 Oct 17. doi:10.1016/S1473-3099(17)30540-6. [Epub ahead of print]

Background: In the UK, HIV incidence among men who have sex with men (MSM) has remained high for several years, despite widespread use of antiretroviral therapy and high rates of virological suppression. Pre-exposure prophylaxis (PrEP) has been shown to be highly effective in preventing further infections in MSM, but its cost-effectiveness is uncertain.

Methods: **In this modelling study and economic evaluation, we calibrated a dynamic, individual-based stochastic model, the HIV Synthesis Model, to multiple data sources** (surveillance data provided by Public Health England and data from a large, nationally representative survey, Natsal-3) **on HIV among MSM in the UK. We did a probabilistic sensitivity analysis** (sampling 22 key parameters) **along with a range of univariate sensitivity analyses to evaluate the introduction of a PrEP programme with sexual event-based use of emtricitabine and tenofovir for MSM who had condomless anal sexual intercourse in the previous 3 months, a negative HIV test at baseline, and a negative HIV test in the preceding year. The main model outcomes were the number of HIV infections, quality-adjusted life-years (QALYs), and costs.**

Findings: **Introduction of such a PrEP programme, with around 4000 MSM initiated on PrEP by the end of the first year and almost 40 000 by the end of the 15th year, would result in a total cost saving** (£1.0 billion discounted), **avert 25% of HIV infections** (42% of which would be directly because of PrEP), **and lead to a gain of 40 000 discounted QALYs over an 80-year time horizon. This result was particularly sensitive to the time horizon chosen, the cost of antiretroviral drugs** (for treatment and PrEP), **and the underlying trend in condomless sex.**

Interpretation: **This analysis suggests that the introduction of a PrEP programme for MSM in the UK is cost-effective and possibly cost-saving in the long term.** A reduction in the cost of antiretroviral drugs (including the drugs used for PrEP) would substantially shorten the time for cost savings to be realised.

[Abstract access](#)

Next generation PrEP—multipurpose technologies in macaques

Editor's notes: *Adherence is an issue not only for oral PrEP but also for topical PrEP. Two large studies of an intra-vaginal ring releasing dapivirine both showed some overall efficacy in the primary analysis, but suggested that very high adherence would be needed to achieve reliable protection from HIV. One reason for poor adherence, particularly among the youngest women in the studies, may be that young women do not seriously consider the chance that they might acquire HIV infection from a romantic partner. Adherence to modern family planning methods has been improved through the use of long-acting reversible products including injections, implants, rings and intra-uterine devices. This has led to enthusiasm for multipurpose technologies that might offer women not only protection against unwanted pregnancies, but also protection from HIV or from other sexually transmitted such as herpes simplex virus. Smith and colleagues present some data from early studies of one such device. They made silicone rings with pods that could deliver hormonal contraception as well as tenofovir alafenamide (against HIV) and acyclovir (against HSV). These rings were shown in macaques to release their different components satisfactorily into the vaginal tissues and systemic circulation at levels that would be predicted to be highly effective. Modern contraceptives are highly effective and hugely important as a means for women to regulate their own fertility. As has been seen with the dapivirine ring studies, adherence to intravaginal products is likely not be as high as can be achieved with injections or implants. So the balance between contraceptive efficacy and the potential benefits of additional prevention tools for HIV and other sexually transmitted infections will need to be weighed carefully. On the other hand, the increasing worry that DMPA may actually increase the risk*

of HIV acquisition (as discussed in previous issues) makes research to broaden the choices for women's reproductive and sexual health even more important.

Novel multipurpose pod-intravaginal ring for the prevention of HIV, HSV, and unintended pregnancy: Pharmacokinetic evaluation in a macaque model.

Smith JM, Moss JA, Srinivasan P, Butkyavichene I, Gunawardana M, Fanter R, Miller CS, Sanchez D, Yang F, Ellis S, Zhang J, Marzinke MA, Hendrix CW, Kapoor A, Baum MM. *PLoS One*. 2017 Oct 5;12(10):e0185946. doi: 10.1371/journal.pone.0185946. eCollection 2017.

Globally, women bear an uneven burden for sexual HIV acquisition. Results from two clinical trials evaluating intravaginal rings (IVRs) delivering the antiretroviral agent dapivirine have shown that protection from HIV infection can be achieved with this modality, but high adherence is essential. Multipurpose prevention technologies (MPTs) can potentially increase product adherence by offering protection against multiple vaginally transmitted infections and unintended pregnancy. **Here we describe a coitally independent, long-acting pod-IVR MPT that could potentially prevent HIV and HSV infection as well as unintended pregnancy. The pharmacokinetics of MPT pod-IVRs delivering tenofovir alafenamide hemifumarate (TAF2) to prevent HIV, acyclovir (ACV) to prevent HSV, and etonogestrel (ENG) in combination with ethinyl estradiol (EE), FDA-approved hormonal contraceptives, were evaluated in pigtailed macaques (N = 6) over 35 days.** Pod IVRs were exchanged at 14 days with the only modification being lower ENG release rates in the second IVR. Plasma progesterone was monitored weekly to determine the effect of ENG/EE on menstrual cycle. The mean in vivo release rates (mg d⁻¹) for the two formulations over 30 days ranged as follows: TAF2 0.35-0.40; ACV 0.56-0.70; EE 0.03-0.08; ENG (high releasing) 0.63; and ENG (low releasing) 0.05. Mean peak progesterone levels were 4.4 ± 1.8 ng mL⁻¹ prior to IVR insertion and 0.075 ± 0.064 ng mL⁻¹ for 5 weeks after insertion, suggesting that systemic EE/ENG levels were sufficient to suppress menstruation. **The TAF2 and ACV release rates and resulting vaginal tissue drug concentrations (medians: TFV, 2.4 ng mg⁻¹; ACV, 0.2 ng mg⁻¹) may be sufficient to protect against HIV and HSV infection, respectively. This proof of principle study demonstrates that MPT-pod IVRs could serve as a potent biomedical prevention tool to protect women's sexual and reproductive health and may increase adherence to HIV PrEP even among younger high-risk populations.**

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Beyond PrEP—immune technologies for prevention

Editor's notes: *Last month, we discussed developments in antibody technology. This month there is a useful perspective paper in Science from Cohen and Corey that lays out the rationale and history of the development of broadly neutralising antibodies for the prevention of HIV. Animal studies show that lower doses of antibody are needed to prevent HIV infection than to control it after the infection has occurred. However, many animal studies are conducted with a narrow range of viruses in the infecting inoculum. Humans are generally exposed to a whole swarm of viruses, meaning that greater breadth of coverage may be needed to protect from infection. Nonetheless, the rapid advances in synthesis of molecules that have additional active sites, such as the bioengineered triphasic antibody, combined with the ongoing proof of concept studies such as antibody-mediated prevention (AMP) mean that we can hope that biomedical prevention beyond PrEP is only just over the horizon.*

Broadly neutralizing antibodies to prevent HIV-1.

Cohen MS, Corey L. *Science*. 2017 Oct 6;358(6359):46-47. doi: 10.1126/science.aap8131.

Advances in technology—especially single-cell antibody cloning techniques—have led to the isolation and characterization of antibodies from people with HIV infection that can neutralize many variants. These are referred to as broadly neutralizing antibodies (bnAbs). Such antibodies can be detected in about 25% of persons with untreated HIV-1 infection, reflecting a host immune response to unremitting viral replication, generation of large numbers of viral variants, and shifting antigen exposure. Although bnAbs may exert some selective pressure as they develop, they generally do not reduce viral burden, improve health, or slow the progression of disease. However, they offer considerable opportunities for treatment and prevention of HIV-1 infection in others. At this time, hundreds of bnAbs have been identified; those that have attracted the most attention are bnAbs with the greatest breadth, neutralizing the largest number of HIV-1 strains, including those traditionally most neutralization resistant; or bnAbs that have the greatest potency, requiring the smallest concentration to neutralize resistant strains of HIV-1.

[Abstract access](#)

3. Key populations

Most HIV transmission occurs within households or within communities, even among highly mobile fishing communities around Lake Victoria.

Editor's notes: *It is well recognized that the fishing communities around Lake Victoria have high HIV prevalence. Fishermen move around to find the best yield and women who buy and sell fish often meet the boats at different fishing villages and may also trade sex for the best fish to maximize their business. It is therefore, perhaps, surprising that Kiwuwa-Muyingo and colleagues' study of the phylogenetics of HIV in five distinct fishing communities in Uganda shows that 83% of the transmission events occur in the context of either household or the local community. Transmission between the communities was less common than expected. On the other hand, many isolates of HIV could not be linked to another isolate in the study, suggesting that they had been imported into the region, or that their transmission cluster had not been sampled. A major challenge for molecular epidemiology studies is that limited coverage of the sampling means that unique isolates might have become linked isolates if the sampling had included more of the population. The authors of this study estimate that they included approximately 44% of all HIV positive individuals in this study cohort, which is similar or better than many phylogenetic studies, but still leaves a lot of room for misclassification biases. A strength of the study was that the authors also included HIV isolates from individuals who had been HIV-negative and followed up over an 18-month period. Among the 34 transmission clusters, 11 included at least one incident case. Although the numbers become too small to be confident, they found that in 36% (4) of these 11 clusters, transmission was likely from one incident case to another incident case. This is an important observation as it highlights the ongoing spread of HIV from recent infection. Transmission of this sort is harder to prevent through the scale up of treatment as it would require people to be tested very regularly, to start treatment before their partner was infected too. Another interesting observation, again based on limited numbers, is that HIV subtype C was more likely to be involved in transmission clusters than subtype A, which in turn was more commonly in clusters than subtype D. Subtype C is not so common and presumably imported into these communities, whereas subtypes A and D are the most common subtypes. We are still in the early days of phylogenetics among African isolates of HIV and many studies have*

significant limitations, so interpretation needs to be cautious. Nonetheless, these techniques will increasingly shed light on the complex and sometimes unexpected interactions between individuals, communities, occupations, migration and HIV subtypes. These insights should help us to focus our HIV prevention and treatment efforts to maximize their impact in the future.

HIV-1 transmission networks in high risk fishing communities on the shores of Lake Victoria in Uganda: A phylogenetic and epidemiological approach.

Kiwuwa-Muyingo S, Nazziwa J, Ssemwanga D, Ilmonen P, Njai H, Ndembi N, Parry C, Kitandwe PK, Gershim A, Mpendo J, Neilsen L, Seeley J, Seppälä H, Lyagoba F, Kamali A, Kaleebu P. PLoS One. 2017 Oct 12;12(10):e0185818. doi:10.1371/journal.pone.0185818. eCollection 2017.

Background: Fishing communities around Lake Victoria in sub-Saharan Africa have been characterised as a population at high risk of HIV-infection.

Methods: Using data from a cohort of HIV-positive individuals aged 13-49 years, enrolled from 5 fishing communities on Lake Victoria between 2009-2011, we sought to identify factors contributing to the epidemic and to understand the underlying structure of HIV transmission networks. Clinical and socio-demographic data were combined with HIV-1 phylogenetic analyses. HIV-1 gag-p24 and env-gp-41 sub-genomic fragments were amplified and sequenced from 283 HIV-1-infected participants. Phylogenetic clusters with ≥ 2 highly related sequences were defined as transmission clusters. Logistic regression models were used to determine factors associated with clustering.

Results: Altogether, 24% (n = 67/283) of HIV positive individuals with sequences fell within 34 phylogenetically distinct clusters in at least one gene region (either gag or env). Of these, 83% occurred either within households or within community; 8/34 (24%) occurred within household partnerships, and 20/34 (59%) within community. 7/12 couples (58%) within households clustered together. Individuals in clusters with potential recent transmission (11/34) were more likely to be younger 71% (15/21) versus 46% (21/46) in un-clustered individuals and had recently become resident in the community 67% (14/21) vs 48% (22/46). Four of 11 (36%) potential transmission clusters included incident-incident transmissions. Independently, clustering was less likely in HIV subtype D (adjusted Odds Ratio, aOR = 0.51 [95% CI 0.26-1.00]) than A and more likely in those living with an HIV-infected individual in the household (aOR = 6.30 [95% CI 3.40-11.68]).

Conclusions: A large proportion of HIV sexual transmissions occur within house-holds and within communities even in this key mobile population. The findings suggest localized HIV transmissions and hence a potential benefit for the test and treat approach even at a community level, coupled with intensified HIV counselling to identify early infections.

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4. Financing

Health economics of HIV in South Africa

Editor's notes: *There is enormous financial pressure on the HIV response. Advances in science had demonstrated the importance of offering treatment to all people living with HIV with ARV medicines and starting treatment as early as possible. In addition to stronger condom programming, biomedical prevention tools, such as medical male circumcision, PrEP have also been shown to be highly efficacious for HIV prevention. Yet international donor support for HIV is no longer increasing and*

national governments are increasingly having to find budgets with a tight fiscal envelope. It is clear that we need innovation, efficiency and strong advocacy for continuing investment to take us to the end of AIDS as a public health threat by 2030. Health economists often use a threshold related to the GDP of a country in order to determine whether investments are cost-effective or not. However, as Meyer-Rath and colleagues point out, this threshold can seem arbitrary and unlinked from the actual budget available to the HIV programme. The authors use their model of the costs and impact of a range of interventions in the South African national programme. They explore both the most cost-effective sequence of interventions, and the cost-effectiveness thresholds that these imply, within the overall budget envelope that has been committed to the HIV response by the government. They propose that within the existing budget of around US\$1.6 billion per year, maximizing scale-up of the most cost-effective interventions would use the entire budget before some of the more expensive options (such as PrEP) were introduced. The authors find that the cost-effectiveness threshold at which the budget is exhausted is between US\$ 547 and US\$ 872 per life-year saved. This compares poorly with the GDP of South Africa of around US\$ 6000 which is often used as a benchmark for cost-effectiveness. This paper confronts us with hard conclusions from a South African perspective. It emphasizes the need to find ways to reduce costs and to maximize funding for HIV. If we do not manage to reduce the epidemic now, the costs in the future will be even higher.

Revealed willingness-to-pay versus standard cost-effectiveness thresholds: evidence from the South African HIV investment case.

Meyer-Rath G, van Rensburg C, Larson B, Jamieson L, Rosen S. PLoS One. 2017 Oct 26;12(10):e0186496. doi: 10.1371/journal.pone.0186496. eCollection 2017.

Background: The use of cost-effectiveness thresholds based on a country's income per capita has been criticized for not being relevant to decision making, in particular in middle-income countries such as South Africa. The recent South African HIV Investment Case produced an alternative cost-effectiveness threshold for HIV prevention and treatment interventions based on estimates of life years saved and the country's committed HIV budget.

Methods: **We analysed the optimal mix of HIV interventions over a baseline of the current HIV programme under the committed HIV budget for 2016-2018. We calculated the incremental cost-effectiveness ratio (ICER) as cost per life-year saved (LYS) of 16 HIV prevention and treatment interventions over 20 years (2016-2035). We iteratively evaluated the most cost effective option (defined by an intervention and its coverage) over a rolling baseline to which the more cost effective options had already been added, thereby allowing for diminishing marginal returns to interventions.** We constrained the list of interventions to those whose combined cost was affordable under the current HIV budget. **Costs are presented from the government perspective, unadjusted for inflation and undiscounted, in 2016 USD.**

Results: **The current HIV budget of about US\$1.6 billion per year was sufficient to pay for the expansion of condom availability, medical male circumcision, universal treatment, and infant testing at 6 weeks to maximum coverage levels, while also implementing a social and behavior change mass media campaign with a message geared at increasing testing uptake and reducing the number of sexual partners.** The combined ICER of this package of services was US\$547/ LYS. The ICER of the next intervention that was above the affordability threshold was US\$872/LYS.

Conclusions: **The results of the South African HIV Investment Case point to an HIV cost-effectiveness threshold based on affordability under the current budget of US\$547-872 per life year saved, a small fraction of the country's GDP per capita of about US\$6000.**

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