In what circumstances could nondaily preexposure prophylaxis for HIV substantially reduce program costs?

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Objectives: To review the main factors influencing the costs of nondaily oral preexposure prophylaxis (PrEP) with tenofovir (\emph{C6}emtricitabine). To estimate the cost reductions possible with nondaily PrEP compared with daily PrEP for different populations (MSM and heterosexual populations).

Design: Systematic review and data triangulation.

Methods: We estimated the required number of tablets/person/week for dosing regimens used in the HPTN 067/ADAPT (daily/time-driven/event-driven) and IPERGAY (on-demand) trials for different patterns of sexual intercourse. Using trial data, and behavioural and cost data obtained through systematic literature reviews, we estimated cost savings resulting from tablet reductions for nondaily versus daily oral PrEP, assuming 100% adherence.

Results: Among different populations being prioritized for PrEP, the median reported number of days of sexual activity varied between 0 and 2 days/week (0–1.5 days/week for MSM, 1–2 days/week for heterosexual populations). With 100% adherence and two or fewer sex-days/week, HPTN 067/ADAPT nondaily regimens reduced the number of tablets/week by more than 40% compared with daily PrEP. PrEP program costs were reduced the most in settings with high drug costs, for example, by 66–69% with event-driven PrEP for French/US populations reporting on average one sex-day/week.

Conclusion: Nondaily oral PrEP could lower costs substantially (>50%) compared with daily PrEP, particularly in high-income countries. Adherence and efficacy data are needed to determine cost-effectiveness.

Keywords: cost savings, oral medicine, preexposure prophylaxis, prevention of sexual transmission, sexual behaviour, tenofovir

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Introduction

Preexposure prophylaxis (PrEP) using oral tenofovir (TDF) [± emtricitabine (FTC)] reduces the risk of acquiring HIV [1]. However, PrEP roll-out can be hampered by concerns about expense and cost-effectiveness. As HIV funding has declined in recent years [2], cost-savings in HIV treatment and prevention are urgently needed. Prioritization of PrEP to groups at higher risk of HIV acquisition improves cost-effectiveness for PrEP interventions [3,4]. Another potential cost-saving strategy is the use of nondaily (or intermittent) oral PrEP regimens based on potential HIV exposures, which are expected to require fewer tablets than daily PrEP. Most clinical trials of oral PrEP have used daily dosing, which is currently recommended by the CDC and FDA, but the IPERGAY (Intervention Préventive de l’Exposition aux Risques avec et pour les Gays) trial, amongst MSM in France and Canada, recently showed effectiveness for nondaily PrEP [5].

So far, the safety and adherence of nondaily oral PrEP has been evaluated in MSM, heterosexual sero-discordant couples, female sex workers, and women living in areas with high HIV incidence [5–8]. Different nondaily PrEP regimens, based upon regimens offering protection in animal studies [9], have been proposed and tested. The HPTN 067/ADAPT trial evaluated the feasibility and acceptability of two nondaily PrEP-dosing strategies: ‘time-driven’ dosing (one tablet twice per week with one tablet after sexual intercourse) and ‘event-driven’ dosing (one tablet before and one tablet after sex), as well as daily dosing [10]. IPERGAY prescribed two tablets together before sex, and two tablets after, 24 h apart [5]. An earlier International AIDS Vaccine Initiative (IAVI) trial of nondaily PrEP in Kenya and Uganda also used time-driven dosing [6,7].

Adherence to nondaily oral PrEP requires taking tablets after sexual intercourse, and may require predicting or planning the occurrence of sexual intercourse in advance. Adherence to nondaily PrEP regimens is expected to influence effectiveness. Full cost-effectiveness estimates for nondaily oral PrEP will need to take into account effectiveness (which is influenced by adherence and efficacy), as well as any reductions in costs resulting from the reduced number of tablets required. Nonetheless, much can be learned from deriving the maximum reduction in program costs that could be achieved with nondaily oral PrEP regimens under ideal conditions of 100% adherence.

In this study, we aimed to determine for which populations and patterns of sexual behaviour nondaily oral PrEP would substantially reduce the overall costs of PrEP delivery programs, compared with daily regimens, if each regimen was used exactly as prescribed. We reviewed and synthesized studies providing information on the main factors influencing the relative cost of nondaily PrEP programs: dosing requirements for regimens used in two recent nondaily oral PrEP trials (HPTN 067/ADAPT and IPERGAY), frequency of sex in priority populations, and PrEP program costs and the proportion of costs attributable to oral PrEP drugs. We combined this information to estimate potential cost reductions for nondaily compared with daily oral PrEP.

Methods

The study was conducted in four stages, determining: the number of tablets required for different nondaily oral PrEP regimens, sexual activity patterns for populations being considered for nondaily PrEP, and PrEP program costs, in order to estimate potential cost-savings for nondaily oral PrEP.

Number of tablets required for each regimen

First, we examined four TDF/FTC PrEP regimens used in HPTN 067/ADAPT [10] and IPERGAY [5], two recently conducted nondaily oral PrEP trials. For each regimen, assuming 100% adherence and accurate prediction of sexual activity, we calculated the weekly number of tablets required per person for different patterns of sexual intercourse, which depends on the number and distribution of days per week when sexual intercourse occurs (sex-days/week).

Sexual activity patterns

Second, we determined sexual activity patterns for populations being considered for nondaily PrEP both from HPTN 067/ADAPT trial data, and through a systematic literature review.

Primary data analysis, HPTN 067/ADAPT

HPTN 067/ADAPT was a phase II, randomized, open-label, pharmacokinetic and behavioural equivalence study of daily versus nondaily oral FTC/TDF PrEP [8,11,12]. The study enrolled HIV-uninfected men and transgender women who have sex with men, aged at least 18 years, in Bangkok, Thailand, and Harlem in New York City, USA, and heterosexual women at high risk for HIV infection in Cape Town, South Africa, aged at least 18 years. The study was conducted with the understanding and consent of each participant. Ethics committee approvals were obtained from the Ethical Review Committee for Research in Human Subjects of the Thailand Ministry of Public Health; the Institutional Review Board of the US Centers for Disease Control and Prevention; the Ethics Committee of the Health Science Faculty, University of Cape Town; the Emavundleni Community Advisory Board and the Medicines Control Council of South Africa; and Columbia University Medical Center. The protocol was registered at ClinicalTrials.gov NCT01327651 and is available at https://www.hptn.org/research/studies/82.
For each population, we calculated the median and interquartile range (25th and 75th percentiles) of sex-days per week (counting only days on which participants reported anal or vaginal sex), pooled across PrEP regimens.

Systematic review of sexual behaviour
We searched PubMed and Web of Knowledge databases for articles published between 1 January 2010 and 31 December 2015 (the first oral PrEP trial results were released in 2010 [13]). Conference abstracts for the 2014 and 2015 CROI and International AIDS Society conferences were searched online.

The search terms were (PrEP OR ‘pre-exposure prophylaxis’) AND (intermittent* OR non-daily OR nondaily OR coitally-related OR ‘fixed dose’ OR post-coital OR ‘on demand’ OR event-based OR event-driven OR time-driven OR weekly-based OR routine OR periodic).

To be eligible for inclusion in the sexual behaviour analysis, studies had to report sexual activity as frequency of sex-days per unit time. Where different articles referred to the same study population, the most recent data were extracted.

The following data were extracted by one investigator: country, study population and design, number of sex-days per unit time (median or categorical data), spacing of sex-days. The median and interquartile range for the frequency of sex-days was calculated from the data provided. If this information was not available, it was requested from study authors.

Oral preexposure prophylaxis program costs
Third, we systematically searched the literature on PrEP program costs. We searched PubMed and Web of Knowledge databases for articles published between 1 January 2010 and 31 December 2015, and searched 2014 and 2015 CROI and International AIDS Society conference abstracts.

The search terms were HIV AND (PrEP OR ‘pre-exposure prophylaxis’) AND cost.

We additionally included data from a study presented at the 2015 Public Health Science conference [14].

To be included, studies had to give the costs of PrEP programs, specify nondrug and drug costs, and allow us to derive the costs of PrEP/person/year.

The following data were extracted by one investigator: country of study, study population, year, total costs/person/year, costs of drugs and/or proportion of costs attributable to drugs, currency. Costs were converted from other currencies into US$ for the same year using the CCEMG–EPPI-Centre Cost Converter [15], using Purchasing Power Parity conversion factors from the International Monetary Fund. Because of the large differences seen in costs between high income countries (HIC) and low and middle-income countries (LMICs), we summarized costs separately for HIC, upper middle-income countries (UMIC), lower middle-income countries (L-MIC) and low-income countries (LIC), following World Bank 2017 classifications [16].

Cost-saving estimates
Fourth, using the data collected in the previous three sections, we estimated the range of cost savings possible because of tablet reductions compared with daily PrEP, assuming 100% adherence, as follows:

\[
\text{Minimum cost saving} = \frac{\text{cost}_\text{proportion-min}}{\text{DDtablets}} \times \left( \frac{\text{NDtablets}_{\text{max}} - \text{NDtablets}_{\text{min}}}{\text{DDtablets}} \right)
\]

\[
\text{Maximum cost saving} = \frac{\text{cost}_\text{proportion-max}}{\text{DDtablets}} \times \left( \frac{\text{DDtablets} - \text{NDtablets}_{\text{min}}}{\text{DDtablets}} \right)
\]

where \( \text{cost}_\text{proportion-min}/\text{cost}_\text{proportion-max} \) = minimum/maximum percentage of costs attributable to PrEP drugs, \( \text{DDtablets} \) = tablets required per week with daily dosing, and \( \text{NDtablets}_{\text{max}}/\text{NDtablets}_{\text{min}} \) = minimum/maximum tablets required per week with nondaily dosing. The number of tablets was estimated using the median number of sex-days/week. Wherever data on the full distribution of sex-days/week were available, the number of tablets were also estimated summing across the distribution. In sensitivity analysis, we used each of the full distributions of sex-days/week obtained for other settings to assess potential cost-savings for each setting which had both cost and behaviour data. Additionally, we calculated hypothetical cost-savings for different frequencies of sex-days/week for four countries with different estimates of the proportion of costs attributable to PrEP drugs.

Results

Number of tablets required for each regimen
In HPTN 067/ADAPT, participants were randomized to one of three PrEP regimens: daily, time-driven, or event-driven TDF/FTC PrEP. Those randomized to daily PrEP were prescribed one tablet per day. The time-driven arm was prescribed one tablet 2 days per week with one tablet within 2 h after sexual intercourse. The event-driven arm was prescribed one tablet between 24 and 48 h before sexual intercourse and a second tablet within 2 h after sex [10].

IPERGAY used an on-demand regimen. Participants were prescribed two tablets together 2–24 h before sexual intercourse, and a third and fourth tablet 24 and 48 h after the first two, respectively [5].
For further details see Supplementary Appendix 1, http://links.lww.com/QAD/B228 and Supplementary Figure 1, http://links.lww.com/QAD/B228.

For 0, 1, and 2 weekly sex-days, 0, 2, and 3–4 weekly tablets, respectively, are required with HPTN 067/ADAPT event-driven dosing (Fig. 1a).

Time-driven dosing requires more tablets than event-driven dosing for 0 sex-days, but similar numbers for 1 or 2 weekly sex-days.

IPERGAY dosing requires no tablets for 0 sex-days/week. For at least one sex-day per week, at least as many weekly tablets are required as with either event-driven or time-driven PrEP (Fig. 1b).

Sexual activity patterns

The systematic review identified 207 unique articles and conference abstracts, of which 14 provided sexual behaviour data, describing 10 populations (7 MSM, 3 heterosexual) in seven independent studies (Supplementary Figure 2a, http://links.lww.com/QAD/B228, Supplementary Table 1, http://links.lww.com/QAD/B228). The median number of sex-days/week was requested and received from authors for two studies [17,18].

| Study          | Country     | Study type | Population          | Median [IQR] |
|----------------|-------------|------------|---------------------|--------------|
| Mutua 2012     | Kenya       | PC−RCT     | MSM − daily PrEP    | 1.4 [0.4–2.5]|
| Holtz 2015     | Thailand    | P2−RCT     | MSM                 | 0.7 [0.4–1.9]|
| Mannheimer 2015| US          | P2−RCT     | MSM                 | 0.0 [0.0–1.0]|
| Volk 2012      | US          | C−S        | MSM                 | 0.0 [0.0–1.0]|
| van Griensven 2010 | Thailand | C−S (within P−C) | MSM | 1.0 [0.0–1.0]|
| Lorente 2012   | France      | C−S        | MSM                 | 1.0 [0.0–2.0]|
| Parsons 2015   | US          | P−C        | MSM                 | 1.5 [1.0–2.3]|
| Kibengo 2013   | Uganda      | PC−RCT     | SHC − daily PrEP    | 1.4 [1.0–1.9]|
| Bekker 2015    | South Africa| P3−RCT     | HW                  | 1.6 [0.8–2.4]|
| Mark 2012      | South Africa| C−S        | HWM                 | 1.0 [0.0–2.0]|

Fig. 1. Tablets required per person in a given week for different number and pattern of sex-days per week assuming 100% regimen adherence and accurate forecasting of sexual behaviour – patterns giving maximum and minimum tablet numbers are shown. (a) Regimens from HPTN 067/ADAPT: event-driven dosing (EDD), time-driven dosing (TDD), daily dosing (DD); (b) IPERGAY on-demand regimen. Daily dosing is shown as a horizontal line, other regimens as bars.

Fig. 2. Forest plot showing median and inter-quartile range (IQR; 25th and 75th percentile) number of days per week sexual activity reported in different populations identified in systematic literature search. PC-RCT, placebo-controlled randomized controlled trial nondaily versus daily PrEP; P2-RCT, phase II randomized controlled trial nondaily versus daily PrEP; C-S, cross-sectional study; P-C, prospective cohort; SHC, sero-discordant heterosexual couples; HW, heterosexual women; HWM, heterosexual women and men.
The median number of sex-days varied between 0 and 1.5 per week for MSM populations from France, Thailand, Kenya, and the United States [6,11,12,17–20] and between 1 and 2 for heterosexual populations from Uganda and South Africa [7,8,21] (Fig. 2, Supplementary Table 1, http://links.lww.com/QAD/B228). Three MSM studies showed variation in number of sex-days/week among respondents, with a few reporting daily sex, but many reporting no sex at all [17,19,20] (Supplementary Table 1, http://links.lww.com/QAD/B228).

Five studies found sex was most likely to be reported at the weekend [17–21], but also frequently occurred on weekdays (Supplementary Table 1, http://links.lww.com/QAD/B228).

**Oral preexposure prophylaxis program costs**

The systematic review identified 222 unique papers and conference abstracts, of which 18, covering 17 independent studies, provided cost data (Supplementary Figure 2b, http://links.lww.com/QAD/B228, Table 1, http://links.lww.com/QAD/B228). Six studies came from HIC, five from UMIC, five from L-MIC, and one from LIC.

The nondrug costs included varied considerably between studies (Table 1). Most studies (16/17) explicitly costed laboratory tests. Specific tests mentioned usually included HIV testing and serum creatinine. Sexually transmitted infection (STI), hepatitis B, pregnancy, and blood urea tests were included less frequently. Staff costs were mentioned in most (12/17) studies. Specific staff roles frequently mentioned were physicians, laboratory staff, and nurses. Three studies each included staff training and adherence counselling costs. Other costs mentioned in one or two studies included condom provision, risk reduction counselling, building, and facilities costs (Table 1). Drug costs from some studies included pharmacy-dispensing fees – wherever these were given separately

In studies from high-income countries (n = 6), drug costs were high (US$6160–17 130/person/year), and accounted for 81–96% of PrEP program costs (Table 1) [14,22–26].

In LMICs (n = 11), drug costs varied between US$50–600/person/year [27–37]. Costs were higher in LMICs outside Africa (US$420–600/person/year; n = 2) than in Africa (US$50–134 for ‘real world’ settings, US$304 in a demonstration project; n = 9). Eight LMIC studies estimated that 21–75% of total PrEP costs were attributable to drugs [27,29–32,35–37], whereas three studies in LMICs estimated that drugs accounted for 89–95% of program costs [28,33,34] (Table 1).

The proportion of costs attributable to drugs tended to be higher in UMIC then in LIC or L-MIC, and was generally higher in countries with high drug costs (Fig. 3). Neither drug costs nor the proportion of costs attributable to PrEP drugs changed significantly over time (not shown).

**Cost-saving estimates**

Supplementary Figure 3, http://links.lww.com/QAD/B228 shows the hypothetical cost savings for different frequencies of sex-days/week and nondaily PrEP regimens in different settings.

For four settings with both cost and behaviour data (MSM in the United States, France, and Kenya, heterosexuals in South Africa), we estimated the cost savings achievable with nondaily compared with daily oral PrEP.

Using the median number of sex-days/week, program costs were reduced the most – by 66–69% – for lower-activity (median one sex-day/week) US or French MSM taking event-driven PrEP (Table 2). The reduction in costs was more modest in settings where drug costs accounted for a smaller proportion of program costs. For example, only a 9–15% reduction was predicted for MSM in Kenya. Cost reductions were also more modest in populations with more frequent sexual activity. When using median sex-days/week, the IPERGAY regimen gave smaller cost-reductions than the HPTN 067/ADAPT regimens, because of the smaller reductions in tablets required.

However, for MSM in France, using data on the full distribution of sex-days across the week gave slightly different estimated savings from using the median number of sex-days. Using the full distribution suggested slightly greater savings with event-driven PrEP, slightly lower savings with time-driven PrEP, but somewhat larger savings with the IPERGAY regimen than when only the median number of sex-days was used (IPERGAY: 50–64% reduction considering the full distribution versus 41–55% using the median). The full distribution of sex-days/week was not available for the other settings with cost data.

In sensitivity analysis, we used each distribution of sex-days/week found in the literature review, all having median one sex-day/week (Supplementary Table 1, http://links.lww.com/QAD/B228), to estimate cost savings for the populations in Table 2, assuming their sexual activity followed these distributions. Using the full distributions rather than the median slightly reduced cost-savings with time-driven PrEP (by up to four percentage points) and somewhat increased cost-savings for event-driven and IPERGAY regimens (up to 5 and 14 percentage points, respectively). Greater increases in cost-savings were seen for distributions with a greater proportion of men reporting no sex-days/week (Supplementary Figure 4, http://links.lww.com/QAD/B228). Full distributions were not available for populations reporting more than a median one sex-day/week.
Table 1. Estimated costs of preexposure prophylaxis programs, and proportion of costs because of preexposure prophylaxis drugs, from costing and cost-effectiveness studies conducted since 2010, by World Bank country classifications for 2017.

| Reference                  | Population                  | Country               | Cost components                                                                 | Cost units* | PrEP total cost per person per year | PrEP drug cost per person per year | Percentage of total costs attributable to drugs |
|----------------------------|-----------------------------|-----------------------|--------------------------------------------------------------------------------|--------------|-------------------------------------|-----------------------------------|------------------------------------------|
| High-income countries      |                             |                       |                                                                                   |              |                                     |                                   |                                          |
| Juusola et al. [22]        | MSM                         | USA                   | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2010     | 10,237                              | 9,441                             | 92%                                      |
| Horberg and Raymond [23]   | Not specified               | USA                   | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2010     | 11,593 (9,387)                      | 9,396 (7,608)                     | 81%                                      |
| Ouellet et al. [24]        | MSM                         | Canada                | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 10,362 (7,025)                      | 9,597 (6,506)                     | 93%                                      |
| Schenker et al. [25]       | MSM                         | Australia             | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 4,560 (6,544)                      | 4,311 (6,159)                     | 95%                                      |
| Ong et al. [34]            | MSM                         | UK                    | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 6,702 (8,655)                      | 6,437 (7,737)                     | 96%                                      |
| Mabileau et al. [26]       | Discordant couples          | France                | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2011     | 606–828                            | 420–600                            | 66–75%                                   |
| Gomez et al. [27]          | MSM                         | Peru                  | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2010     | 150                                 | 134                                | 89%                                      |
| Pietrus et al. [28]        | General population          | South Africa          | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 252                                 | 118                                | 47%                                      |
| Comin et al. [29]          | General population          | South Anna            | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 95                                  | 50                                 | 51%                                      |
| Stover et al. [30]         | General population          | South Africa          | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 148                                 | 75                                 | 51%                                      |
| Walensky et al. [31]       | High-risk women             | South Africa          | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 618 1st year; 522 2nd year          | 110 1st year; 21% 2nd year          | 37%                                      |
| Lower-middle income countries |                             |                       |                                                                                   |              |                                     |                                   |                                          |
| Alistar et al. [32]        | People who inject drugs     | Ukraine               | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 233                                 | 96                                 | 39%                                      |
| Nichols et al. [33]        | General population          | Zambia                | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 618 1st year; 522 2nd year          | 110 1st year; 21% 2nd year          | 37%                                      |
| Nichols et al. [34]        | General population          | Zambia                | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 233                                 | 96                                 | 39%                                      |
| Kiraga et al. [35]         | MMM and young women         | Kenya                 | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 618 1st year; 522 2nd year          | 110 1st year; 21% 2nd year          | 37%                                      |
| Mitchell et al. [36]       | Discordant couples          | Nigeria               | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 618 1st year; 522 2nd year          | 110 1st year; 21% 2nd year          | 37%                                      |
| Low-income countries       |                             |                       |                                                                                   |              |                                     |                                   |                                          |
| Ying et al. [37,38]        | Discordant couples          | Uganda                | ARV drugs, laboratory tests, HIV testing, STI testing, B test, hepatitis B test, serum creatinine, pregnancy test, staff costs, laboratory staff, adherence counseling, other costs | US $2012 (US $2012) | 618 1st year; 522 2nd year          | 110 1st year; 21% 2nd year          | 37%                                      |

*Where year is missing, this was not specified in the article.

The drug costs include pharmacist markup and dispensing fees.
In this study, we reviewed the key factors likely to influence what cost reductions could be achieved with nondaily oral PrEP. Our study suggests substantial reductions in required tablets—and therefore costs—could be seen in populations having sexual activity on average 1–2 days a week, a typical level of activity for many populations being prioritized for PrEP around the world. The extent of these cost reductions will partly depend on individuals’ ability to accurately predict or plan sexual activity, and on the proportion of PrEP program costs which are attributable to drug costs.

Current evidence suggests that large cost-savings could be made in high-income countries, where generic PrEP drugs are not available, and high drug costs account for the majority (81–96%) of oral PrEP program costs. We predict that costs could be reduced the most—by at least 50%—for MSM in the United States or France reporting sexual activity on average 1 day per week, using any of the nondaily regimens explored here.

Clustering of sex-days on consecutive days reduces the number of tablets required for event-driven and on-demand regimens, but little information on clustering of sex-days has been collected in studies of populations being considered for nondaily PrEP. It is likely that being in a stable partnership is associated with different patterns of sexual behaviour. We were unable to evaluate this here, as published behavioural data was not stratified by partnership status.

Variation between studies in how costs are described and classified makes it difficult to assess whether all costs are being fully accounted for; if nondrug costs have been underestimated, or drug costs over-estimated, then cost-savings associated with nondaily oral PrEP will be reduced. Estimated drug costs for TDF/FTC have recently declined in many LMICs (including Ukraine and many African countries [39,40]), reducing potential future cost-savings for nondaily versus daily oral PrEP. Drug costs have not declined in HIC, but could decline in future, for example, after drug patents expire. We have not specifically looked at the effects of intellectual property rights and price controls on drug costs, making future predictions more uncertain.

We have assumed that PrEP program nondrug costs will not be affected by the PrEP-dosing regimen; that the same frequency of monitoring, and level of adherence counselling, will be required for nondaily as daily PrEP, and that no additional costs are associated with educating patients about nondaily PrEP use. If this is not true, then the potential cost-savings that could be achieved with nondaily PrEP will be affected.

**Discussion**

Table 2. Estimated cost savings with nondaily PrEP.

| Country        | Population                | Median days/ week have sex | Percentage of costs attributable to PrEP drugs | Cost reductions with EDD | Cost reductions with TDD | Cost reductions with IPERGAY regimen |
|----------------|---------------------------|----------------------------|-----------------------------------------------|--------------------------|----------------------------|--------------------------------------|
| United States  | MSM (lower activity)      | 1                          | 92–96%                                        | 66–69%                   | 53–69%                     | 39–55%                               |
| United States  | MSM (higher activity)     | 1.5                        | 92–96%                                        | 39–69%                   | 39–69%                     | 0–55%                                |
| France         | MSM                       | 1                          | 96%                                           | 69%                      | 55–69%                     | 41–55%                               |
| Kenya          | MSM (using distribution)  |                             | [69–73%]                                     | [52–64%]                 | [50–64%]                   | [50–64%]                             |
| South Africa   | Heterosexual (lower activity) | 1                          | 21%                                          | 15%                      | 12–15%                     | 9–12%                                |
| South Africa   | Heterosexual (higher activity) | 2                          | 47–53%                                       | 34–38%                   | 27–38%                     | 20–30%                               |

EDD, event-driven PrEP; TDD, time-driven PrEP (regimens from HPTN 067/ADAPT). Figures in italics were estimated using the full distribution of sex-days per week across the population, rather than the median.
Two of the behavioural studies identified collected prospective sexual forecasting data [18,41]. In both studies, 57% of those saying they would have sex the following day actually did so. A substantial number of unnecessary tablets were taken by participants prescribed event-driven PrEP in HPTN 067/ADAPT, for example, 1293 for United States MSM, versus 2573 prescribed. If United States MSM prescribed event-driven oral PrEP took 1–1.4 unnecessary tablets for every two prescribed, as implied by these data, this would reduce the cost-reduction in our best-case scenario (prescribing event-driven PrEP for United States MSM having sex on average on 1 day/week) from 66–69% to 47–55%.

In the studies identified, both prospective and retrospective reporting suggested substantial underestimation of when sex would occur [18–21,41]. In HPTN 067/ADAPT and the earlier IAVI trial of nondaily PrEP, adherence was almost always better for daily than nondaily PrEP [6–8,11,12], the only exception being MSM in Bangkok, for whom adherence was comparable in the daily and time-driven arms. Thus effectiveness for nondaily oral PrEP may be lower than that seen with daily dosing. Notably, low adherence to postsex tablets was found for nondaily regimens in both trials [6–8,11,12,42]. However, MSM in the IPERGAY trial had high reductions in HIV incidence [5], demonstrating that nondaily oral PrEP can be effective.

One limitation of this analysis is the small number of studies reporting sexual activity in terms of sex-days per week. This sexual activity metric is the most relevant for nondaily PrEP use but it is not routinely measured (e.g. it was not measured in IPERGAY). In addition, because of a lack of data on the full distribution of sex-days, we used the median frequency of sex-days/week in our cost-reduction estimates to produce comparable estimates across different settings, which may have led to inaccuracies. Sensitivity analysis suggests that this may have underestimated the cost-savings possible with the IPERGAY regimen because of the large proportion of men not reporting any sex in the last week who required no tablets.

This study reviewed the available data on sexual activity and forecasting relevant for nondaily PrEP, and analysed the cost-reductions of nondaily oral regimens in comparison with daily oral PrEP with 100% regimen adherence. It showed that large cost-reductions are possible for populations in high-income countries, although these might be partially attenuated for regimens requiring forecasting of sexual activity, if additional tablets unnecessary for protection are taken. Smaller cost-reductions were predicted for LMICs in Africa, because of the much lower cost of drugs. A lack of cost and behavioural data from the same countries precluded us from drawing conclusions for LMICs in other regions, such as Thailand.

The next step necessary for estimating cost-effectiveness of nondaily oral PrEP is to evaluate the effectiveness of these regimens, for which efficacy as well as adherence to nondaily PrEP will need to be taken into account [43,44].

Estimates for MSM suggest that four doses of oral PrEP per week are sufficient to provide a 96% reduction in HIV risk [45]. As higher regimen adherence is often seen for daily compared with nondaily PrEP, one way to reduce costs for MSM might be to provide blister packs alternating PrEP and nonactive tablets for daily use, akin to the female contraceptive pill. Alternatively, they could be prescribed two tablets on 2 days per week. These regimens could reduce program costs – and improve cost-effectiveness – without reducing effectiveness.

Trials of nondaily oral PrEP amongst women vaginally exposed to HIV have not been powered to detect efficacy, and daily dosing trials have suggested that six to seven PrEP doses per week are needed to provide 94% protection against HIV after vaginal sex [46,47]. Pharmacokinetic/pharmacodynamic modelling suggests that the IPERGAY PrEP regimen should provide good protection for women at the time of sex and for 72 h afterwards, but that drug concentrations in the female genital tract then decline rapidly, meaning that further postsex doses may be required for full protection [47]. Further studies are therefore required to determine whether, and under which regimens, nondaily PrEP could be protective for women.

In conclusion, we have shown that nondaily oral PrEP regimens could theoretically substantially reduce program costs compared with daily PrEP, particularly for populations in high-income countries having sex on average 1 day/week or less. However, lower adherence reported with nondaily regimens, and imperfect prediction of future sexual activity, may reduce PrEP effectiveness and/or increase costs. Full cost-effectiveness analysis will be necessary to evaluate the full benefits of nondaily oral PrEP regimens.

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Conflicts of interest
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