**Supplemental digital content**

For ‘In What Circumstances Could Non-daily Pre-exposure Prophylaxis for HIV Substantially Reduce Program Costs?’

By Kate M. Mitchell et al.

**Appendix 1: Full detail on PrEP regimens**

**HPTN 067/ADAPT**

Those randomized to daily PrEP were prescribed one tablet per day. Those in the time-driven arm were prescribed one tablet two days per week, 3–4 days apart, plus one tablet within 2 hours after sexual intercourse. They were instructed not to take further doses if they had more than one sex act on the same day, and the post-exposure tablet counted as one of the twice-weekly doses if it occurred on the prescribed day. Those in the event-driven arm were prescribed one tablet between 24 and 48 hours before sexual intercourse and a second tablet within 2 hours after sex. The post-exposure dose counted as a pre-exposure dose for sex acts occurring up to 48 hours later. Participants in all arms were instructed to take no more than 2 tablets/day or 7 tablets/week.

**IPERGAY**

IPERGAY used an on-demand regimen. Participants were prescribed two tablets together 2 to 24 hours before sexual intercourse, and a 3rd and 4th tablet 24 and 48 hours after the first two, respectively. Where participants had multiple episodes of sexual intercourse on consecutive days, they were instructed to take one tablet/day until the last sexual intercourse, and then take a further two tablets 24 hours apart. When resuming PrEP, they were instructed to take two tablets before sex unless they had taken PrEP in the last 7 days, in which case they should take only one tablet.

**Supplementary Figure 1.** Diagram showing number of tablets required for different PrEP regimens with different spacing of sex-days/week, when having 2 sex-days per week. (a) sex-days spread out (2 days between) and (b) successive sex-days. Note multiple episodes of sexual intercourse on one day do not alter dosing.

**Supplementary Figure 2.** Flow diagram showing search procedure and article selection for (a) behavioural data search and (b) PrEP program costs.

(a)

207 records screened

207 records after duplicates removed

1 additional record identified through article bibliography

299 records identified through database searching

109 from PubMed, 151 from Web of Science, 39 from conferences

182 records excluded

25 full-text articles assessed for eligibility

11 full-text articles excluded

11 had no information about sex-days per unit time

14 articles provided data for quantitative sexual frequency synthesis

10 populations in 7 studies

(b)

1 additional record identified from another conference

334 records identified through database searching

119 from PubMed, 181 from Web of Science, 34 from conferences

222 records after duplicates removed

191 records excluded

222 records screened

13 full-text articles excluded:

6 did not present any cost data

3 presented insufficient cost data

3 did not give separate drug and non-drug costs

1 was a review article

31 full-text articles assessed for eligibility

18 articles provided data for quantitative analysis, from 17 separate studies

**Supplementary Table 1:** Sexual behavioural data for populations being considered for non-daily PrEP. IQR = inter-quartile range (25th and 75th percentiles). Figures in italics are calculated from categorical data.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Reference(s) | Study designa | Populationb | Country | Days of the week on which sex reported | Sex-days reported per week |
| **Categorical data** | **Median** | **IQR** |
| Mutua 2012 [1-4] | PC-RCT of non-daily vs daily PrEP | MSM | Kenya | - |  | Daily PrEP: 1.4Non-daily PrEP: 0.7 | 0.4–2.50.4–1.9 |
| Kibengo 2013 [4, 5] | PC-RCT of non-daily vs daily PrEP | SHC | Uganda | - |  | Daily PrEP: 1.4Non-daily PrEP: 1.6 | 1.0–1.90.8–2.4 |
| HPTN 067/ADAPT; Bekker 2017  | RCT of non-daily vs daily PrEP | Women | South Africa | - |  | 1.0 | 0.0–2.0 |
| HPTN 067/ADAPT; Holtz 2015 [6] | RCT of non-daily vs daily PrEP | MSM | Thailand | - |  | 0.0 | 0.0–1.0 |
| HPTN 067/ADAPT; Mannheimer 2015 [7] | RCT of non-daily vs daily PrEP | MSM | US | - |  | 0.0 | 0.0–1.0 |
| Mark 2012 [8] | C-S preparatory study for trial | Heterosexual women and men | South Africa | Mon 28%Tues 23%Weds 25%Thurs 28%Fri 48%Sat 50%Sun 38% | 0% 7 days | 2.0 | - |
| Volk 2012 [9] | C-S  | MSM | US | Min/max:Weds 14%Sat 18%Consecutive:3 days 1.4%4 days 0.7% | 49% 0 days27% 1 day9% 2 days15% ≥3 days | *1.0* | *0.0–1.0*  |
| Lorente 2012 [10] | C-S preparatory study for trial | MSM | France | Mon 17%Tues 15%Weds 16%Thurs 14%Fri 15%Sat 17%Sun 18% | 42% 0 days29% 1 day13% 2 days6% 3 days5% 4 days2% 5 days0.5% 6 days2% 7 days | 1.0 | 0.0–2.0 |
| Parsons 2015 [11] | P-C | MSM | US | weekend vs weekday OR 1.31, 95% CI 1.00–1.72 | 36% <3 days64% ≥3 days | 1.5 | 1.0–2.3 |
| Van Griensven 2010 [12] | C-S (within P-C) | MSM | Thailand | Mon 27%Tues 22%Weds 25%Thurs 23%Fri 28%Sat 33%Sun 33% | 37% 0 days33% 1 day16% 2 days7% 3 days3% 4 days2% 5 days1% 6 days1% 7 days | *1.0* | *0.0–2.0* |

aStudy type:PC-RCT = placebo-controlled randomized controlled trial; RCT = randomized controlled trial; C-S = cross-sectional study; P-C = prospective cohort; bStudy population: MSM = men who have sex with men; SHC = sero-discordant heterosexual couples

**References for Supplementary Table 1**

1. Mutua G, Sanders E, Mugo P, Anzala O, Haberer JE, Bangsberg D*, et al.* **Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers**. *PLoS One* 2012,**7**:e33103.

2. Van der Elst EM, Mbogua J, Operario D, Mutua G, Kuo C, Mugo P*, et al.* **High acceptability of HIV pre-exposure prophylaxis but challenges in adherence and use: qualitative insights from a phase I trial of intermittent and daily PrEP in at-risk populations in Kenya**. *AIDS Behav* 2013,**17**:2162-2172.

3. Mugo PM, Sanders EJ, Mutua G, van der Elst E, Anzala O, Barin B*, et al.* **Understanding Adherence to Daily and Intermittent Regimens of Oral HIV Pre-exposure Prophylaxis Among Men Who Have Sex with Men in Kenya**. *AIDS Behav* 2015,**19**:794-801.

4. Baxi SM, Liu A, Bacchetti P, Mutua G, Sanders EJ, Kibengo FM*, et al.* **Comparing the novel method of assessing PrEP adherence/exposure using hair samples to other pharmacologic and traditional measures**. *J Acquir Immune Defic Syndr* 2015,**68**:13-20.

5. Kibengo FM, Ruzagira E, Katende D, Bwanika AN, Bahemuka U, Haberer JE*, et al.* **Safety, adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial**. *PLoS One* 2013,**8**:e74314.

6. Holtz TH, Chitwarakorn A, Curlin ME, Hughes J, Amico KR, Hendrix C*, et al.* **HPTN 067/ADAPT study: a comparison of daily and non-daily pre-exposure prophylaxis dosing in Thai men who have sex with men, Bangkok, Thailand**. *J Int AIDS Soc* 2015,**18**:25-26.

7. Mannheimer S, Hirsch-Moverman Y, Loquere A, Franks J, Hughes J, Ou S-S*, et al.* **HPTN 067/ADAPT study: a comparison of daily and intermittent pre-exposure prophylaxis dosing for HIV prevention in men who have sex with men and transgender women in New York city**. *J Int AIDS Soc* 2015,**18**:24-25.

8. Mark D, Amico KR, Wallace M, Roux S, Grant R, Wood R*, et al.* **Acceptability of oral intermittent pre-exposure prophylaxis as a biomedical HIV prevention strategy: results from the South African ADAPT (HPTN 067) Preparatory Study**. *J Int AIDS Soc* 2012,**15**:141.

9. Volk JE, Liu A, Vittinghoff E, Irvin R, Kroboth E, Krakower D*, et al.* **Sexual frequency and planning among at-risk men who have sex with men in the United States: implications for event-based intermittent pre-exposure prophylaxis**. *J Acquir Immune Defic Syndr* 2012,**61**:112-115.

10. Lorente N, Fugon L, Carrieri MP, Andreo C, Le Gall JM, Cook E*, et al.* **Acceptability of an "on-demand" pre-exposure HIV prophylaxis trial among men who have sex with men living in France**. *AIDS Care* 2012,**24**:468-477.

11. Parsons JT, Rendina HJ, Grov C, Ventuneac A, Mustanski B. **Accuracy of highly sexually active gay and bisexual men's predictions of their daily likelihood of anal sex and its relevance for intermittent event-driven HIV pre-exposure prophylaxis**. *J Acquir Immune Defic Syndr* 2015,**68**:449-455.

12. van Griensven F, Thienkrua W, Sukwicha W, Wimonsate W, Chaikummao S, Varangrat A*, et al.* **Sex frequency and sex planning among men who have sex with men in Bangkok, Thailand: implications for pre- and post-exposure prophylaxis against HIV infection**. *J Int AIDS Soc* 2010,**13**:13.

**Supplementary Figure 3.** Estimated cost-savings with non-daily PrEP for different numbers of sex-days per week assuming 100% regimen adherence and accurate forecasting of sexual behaviour. Cost-savings are shown for four different countries with differing estimates of the proportion of PrEP program costs which are attributable to medication costs (% of costs due to medication shown in brackets in the key).(a) Event-driven dosing (EDD) regimen from HPTN 067, with sex days spread out; (b) time-driven dosing (TDD) regimen from HPTN 067, with one sex day coinciding with regular pill; (c) IPERGAY on-demand regimen with sex days spread out and PrEP taken in the previous week.







**Supplementary Figure 4.** Sensitivity analysis of reduction in tablets required and cost savings with non-daily PrEP using information on the full distribution of sex-days per week across the population from other locations, compared with using the median. (a) Distributions of sex-days per week used for the sensitivity analysis: median and using data from three studies of MSM populations (van Griensven et al (Thailand),Lorente et al (France) and Volk et al (US)), all reporting a median of **one sex-day per week**. For the distribution for Volk et al, sex-days for 3+ days/week (not given in the paper; striped bars) were assumed to be distributed in the same proportion as in van Griensven et al. (b) Tablets required per person per week for daily dosing (DD), event-driven dosing (EDD), time-driven dosing (TDD) and IPERGAY on-demand regimens, (c) reduction in number of tablets required for non-daily vs daily dosing, (d-g) reduction in program costs estimated for populations with a median one sex-day/week in (d) France, (e) the United States, (f) Kenya and (g) South Africa, using each of the distributions of sex-days per week from other locations given in (a).







