Lancet HIV Comment on: ‘A radomized open label trial of daily and non-daily pre-exposure prophylaxis in African women: The HPTN 067/ADAPT Cape Town Trial.’

**Title:** Working towards HIV prevention choices for women

**Authors:** Janneke van de Wijgert1,2

**Affiliations:**

1. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
2. Institute of Infection and Global Health, University of Liverpool, Liverpool, UK

In The Lancet HIV Bekker and colleagues report that most women in Crossroads, Cape Town, South Africa took oral pre-exposure prophylaxis (PrEP) for HIV prevention when offered to them in an open-label randomised trial (the HPTN 067/ADAPT Trial) [1]. HIV-negative women aged 18 to 52 (N=178) were randomised 1:1:1 to once daily use (D), time-driven use (T: twice weekly plus a post-sex dose), or event-driven use (E: one dose before and one after sex) of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) oral PrEP for 24 weeks. Rigorous methods were used to determine adherence and sex acts ‘covered’ by drug (Wisepill™ device, weekly interviews to review sexual activity and Wisepill™ data, and drug concentrations in plasma and peripheral blood mononuclear cells). Full coverage (defined as at least one pill within 96 hours before and one pill within 24 hours after vaginal or anal sex by interview/Wisepill™ data) was higher in D (75%) than in T (56%) or E (52%), but there was no difference between the groups when full and partial coverage were combined (D 97%, T 95%, E 93%). Far fewer pills were needed to achieve 100% adherence in T (3,616 pills) and E (2,203 pills) than in D (9,652 pills). Side effects were uncommon in D but less frequent in T and E. The trial was not powered to detect differences in HIV seroconversions between the study groups.

Previous daily oral PrEP placebo-controlled efficacy trials in African women have shown mixed results with two discordant couples trials showing 63-75% efficacy [2, 3], and two trials that enrolled women without their male partners terminated prematurely because of a lack of benefit due to low adherence [4, 5]. As a result, many in the field argued that African women are not interested in using oral PrEP. Trials such as the ADAPT trial were very much needed to test this hypothesis in an open label setting and to determine whether non-daily PrEP regimens might be more feasible and acceptable than daily PrEP. The ADAPT trial clearly showed that many women are interested in oral PrEP when offered to them with information about expected safety and efficacy (with one caveat: efficacy evidence for non-daily PrEP was lacking during trial implementation) and no risk of being randomised to a placebo. This is consistent with trials in men who have sex with men that showed higher oral PrEP efficacy in open-label [6, 7] than placebo-controlled settings [8], and is a major step forward in HIV prevention in women.

The ADAPT trial findings regarding the best dosing strategy are, however, less clear. The authors’ definition of full coverage was based on intracellular half-lives of the active drugs and challenge studies in non-human primates [9, 10], which may not translate to the human situation: women who achieved partial coverage by the authors’ definition might still have been protected from HIV. Qualitative research with ADAPT participants revealed that women in the non-daily groups sometimes had difficulty predicting when and where sex would take place, and as a result, might not always have had access to their pills for pre- and/or post-sex dosing [11]. However, quantitative ADAPT trial data showed that partial coverage was mostly due to missed post-sex dosing [1]. Participants were told that post-sex dosing should preferably take place within two hours post-sex (even though the definition of full coverage was ‘within 24 hours post-sex’), and this was at odds with some women’s wish to relax after sex [11]. Other, much smaller, studies of intermittent PrEP in different populations have also shown that dosing within two hours post-sex is more challenging than daily or pre-sex dosing [12, 13]. Furthermore, the ADAPT trial only studied PrEP use for 24 weeks, and found a decrease in adherence and coverage over time in all three randomisation groups. The challenges associated with post-sex dosing and dosing fatigue over time should be addressed, and much larger trials conducted to determine longer-term adherence, safety and HIV prevention efficacy with different regimens in high frequency versus low frequency sexual risk settings. In parallel, extended-release formulations of antiretroviral drugs (such as vaginal rings and injectables) should continue to be developed; recent successes with tenofovir and dapivirine vaginal rings are encouraging in that regard [14-16].

The family planning field has taught us that one size does not fit all, and that providing women with options will prevent more unintended pregnancies [17]. It is very likely that the same will apply to HIV prevention in women.

**References:**

1. Bekker LG, Roux S, Sebastien E, et al. A randomized open label trial of daily and non-daily pre-exposure prophylaxis in African women: The HPTN 067/ADAPT Cape Town trial. *Lancet HIV*. 2017; in press.
2. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012; **367**: 399-410.
3. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012; **367**: 424-34.
4. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV prevention among African women. *N Engl J Med*. 2012; **367**: 411-22.
5. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2015; **372**: 509-18.
6. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet*. 2016; **387**: 53-60.
7. Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk of HIV-1 infection. *N Eng J Med*. 2015; **373**: 2237-46.
8. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Eng J Med*. 2010; **363**: 2587-99.
9. Garcia-Lerma JG, Otten RA, Qari SH, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. *PLoS Med*. 2008; **5**: e28.
10. Radzio J, Aung W, Holder A, et al. Prevention of vaginal SHIV transmission in macaques by a coitally-dependent Truvada regimen. *PLoS One.* 2012; **7**: e50632.
11. Amico KR, Wallace M, Bekker LG, et al. Experiences with HPTN 067/ADAPT study-provided open-label PrEP among women in Cape Town: facilitators and barriers within a mutuality framework. *AIDS Behav*. 2017; **21**: 1361-75.
12. Mutua G, Sanders E, Mugo P, 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.
13. Kibengo FM, Ruzagira E, Katende D, 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.
14. Abdool Karim Q, Abdool-Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010; **329**: 1168-74.
15. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med*. 2016; **375**: 2121-32.
16. Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. *N Engl J Med*. 2016. **375**: 2133-43.
17. Delany-Moretlwe S, Mullick S, Eakle R, Rees H. Planning for HIV preexposure prophylaxis introduction: lessons learned from contraception. *Curr Opin HIV AIDS*. 2016; **11**: 87-93.