

COMPARISON OF ADHERENCE TO PRE-EXPOSURE PROPHYLAXIS DURING
BLINDED AND OPEN-LABEL PHASES OF A RANDOMIZED TRIAL

JUSTIN BRANTLEY

A thesis submitted in partial fulfillment
of the requirements for the degree of

MASTER OF SCIENCE

University of Washington

2014

Committee:

Jared Baeten
Carey Farquhar

Program Authorized to Offer Degree:

Public Health – Epidemiology

© Copyright 2014
Justin Brantley

ABSTRACT

Comparison of adherence to pre-exposure prophylaxis during
blinded and open-label phases of a randomized trial

Justin Brantley

Chair of the Supervisory Committee:

Associate Professor Jared Baeten

Departments of Global Health and Medicine

Adjunct Associate Professor, Department of Epidemiology

The Partners PrEP Study, a randomized trial of daily oral pre-exposure prophylaxis for HIV prevention, demonstrated efficacy at an interim analysis, prompting discontinuation of its placebo arm and early release of results. Active arm participants continued followup, and placebo arm participants optionally re-consented to additional followup on active drug. We compared PrEP adherence, by multiple measures, during the placebo-controlled and subsequent open-label phases of the study. Learning of PrEP efficacy led to a modest, although statistically significant, increase in adherence: the odds of refilling study medication at each monthly visit increased by 24% ($p = 0.03$), and the odds of detecting PrEP drug in plasma increased by 76% ($p < 0.01$), the latter returning to counterfactual levels within twelve months. Placebo arm participants who chose to continue followup on active drug were more likely to refill than those originally randomized to active drug (odds ratio, 1.32; $p < 0.01$). These results suggest that knowledge of PrEP efficacy had a small impact on PrEP adherence in a trial where adherence was already high.

INTRODUCTION

Pre-exposure prophylaxis (PrEP), using the antiretroviral agent tenofovir disoproxil fumarate (TDF) alone or in combination with emtricitabine (TDF-FTC), is an effective biomedical option for HIV prevention, but adherence to PrEP is necessary for its efficacy. Four clinical trials have demonstrated PrEP efficacy in diverse populations, with HIV protection estimates between 44 and 75 percent in randomized comparisons versus placebo[1–4], but two trials found no evidence of benefit[5, 6]. Adherence was strongly tied to HIV prevention in these trials, and subsequent work has tried to understand reasons for non-adherence in PrEP studies.[7, 8] A number of explanations have been hypothesized: low perception of HIV risk, low acceptance of the product itself or timing of use, stigma related to use of an antiretroviral medication, lack of partner involvement or support, and uncertainty about PrEP efficacy in the context of a randomized, placebo-controlled comparison.[6, 9–16] While each of these potential reasons for non-adherence has important implications for PrEP implementation and for future HIV prevention studies, the last is particularly relevant for clinical trials of novel, yet-unproven prevention products.

The Partners PrEP Study was unique because efficacy was proven at an interim analysis, and study participants continued open-label PrEP thereafter, including those in the placebo arm given the option of re-consenting to additional followup on active PrEP. Thus, the early release of results and discontinuation of the placebo arm created a natural experiment to explore how knowledge of PrEP efficacy may influence adherence to active PrEP. Furthermore, placebo arm participants who chose to re-consent to additional followup may better represent individuals who were motivated to use PrEP. We compared PrEP adherence, using multiple measures, during the placebo-controlled and open-label phases of the Partners PrEP Study.

METHODS

The Partners PrEP Study was a phase III, randomized, double-blind, placebo-controlled clinical trial of daily oral PrEP for prevention of HIV among heterosexual, HIV-serodiscordant couples in Kenya and Uganda. The trial's methods have been detailed previously.[1, 17] Briefly, beginning in 2008 a total of 4,747 couples were enrolled and followed. The HIV-seronegative partner was randomized to receive daily oral tenofovir

(TDF), tenofovir-emtricitabine (TDF-FTC), or matching placebo and attended monthly clinic visits for up to 36 months to receive comprehensive HIV prevention services, be dispensed a new bottle of study medication, and return unused medication from the previous month. Participants were tested monthly for HIV, and study medication was withheld from those who were found to have become HIV-infected. In addition, female participants received monthly pregnancy tests and were placed on a study medication hold if pregnant or breastfeeding. Study medication dispensations, pill counts, and other clinical data were transcribed onto structured case-report forms. The study protocol was approved by institutional review boards at the University of Washington and each study site, and all participants provided written informed consent.

On 10 July 2011, at an interim review, the trial's independent Data and Safety Monitoring Board recommended immediate discontinuation of the placebo arm because the protective effect of PrEP had met prespecified stopping criteria. Participants originally randomized to receive active PrEP continued followup without break, and participants who had been randomized to the placebo arm were given the option of being re-randomized to receive either TDF or TDF-FTC PrEP for an additional twelve months of followup. Of 1,418 participants who were originally randomized to the placebo arm and who were clinically eligible to receive PrEP, 1,264 (89 percent) consented to the additional followup.[18] The present analysis includes data through the end of followup in December 2012.

MEASURES OF ADHERENCE For this analysis, four objective measures of adherence to study medication were assessed: study medication refill (i.e., whether or not medication was dispensed at each monthly, expected clinic visit), pill count of returned unused pills (done monthly), electronic pill bottle monitoring (measured in a subset of participants at three study sites), and detection of tenofovir in blood plasma (measured in a randomly-selected subset of subjects). Comparisons of these four objective measures of adherence before and after July 2011 were conducted among the 3,163 participants who were originally randomized to the active PrEP arms. We performed additional analyses comparing participants re-randomized from the placebo arm of the trial to participants originally randomized to the active arms. As medication adherence is a behavioral measure, analyses focused on followup time when participants were expected to take study medication and were able to do so; accordingly, all models excluded observations that occurred during a protocol-defined study medication hold (e.g., due to pregnancy or clinical adverse event).

For medication refill rates, participants were expected to refill their study medication once per month at scheduled clinic visits and were counted as having refilled if they were issued a bottle of study medication at any time during the month or when they were issued multiple bottles in advance of a planned missed visit. This analysis included all participants and all followup time, except during study medication holds; missed visits were counted as missed refills.

The number of pills taken was estimated as the count of pills dispensed minus the count of pills returned at a subsequent clinic visit. Models of pill counts were conducted using two approaches: first, including all followup time except during medication holds (thus, missed visits and other months with no refill were counted as zero pills taken) and second, excluding months in which the participant had no pills (thus removing missed visits from the analysis).

Three of the nine Partners PrEP Study sites participated in a substudy that used Medication Event Monitoring System (MEMS) caps (Aardex) to electronically record each time a bottle of study medication was opened during the month.[19] Participants who were originally randomized to active PrEP continued to use MEMS caps after July 2011, but MEMS caps were not re-issued to re-randomized placebo participants.

Blood plasma specimens from a random sample of participants (100 from the TDF arm, 100 from the TDF-FTC arm, and 100 from placebo arm participants after re-randomization to active PrEP) were assayed for the presence of tenofovir using a previously described liquid chromatography/mass spectrometry procedure.[20, 21] Specimens were collected at study months 1, 3, 6, 12, 18, 24, 30, and 36 for participants originally randomized to active PrEP and at re-randomization months 1, 3, 6, and 12 for participants originally randomized to placebo. Drug was considered present if the concentration of tenofovir was greater than the lower limit of detection of the assay (0.3 ng/mL), consistent with dosing in the last week[22]. We limited analyses of plasma tenofovir concentrations to specimen collections that were preceded by two consecutive weeks during which the participant had medication to take (thus, had not missed a visit).

STATISTICAL ANALYSIS The present analysis tests whether adherence to study medication after July 2011, when all participants knew they were receiving active and efficacious PrEP, differed from adherence during the fully blinded phase of the Partners PrEP Study. To do so, generalized estimating equation (GEE) methods were used to model adherence as a function of calendar time in such a way that the slope and intercept of the model could change at 10 July 2011, the day the positive trial results became known. We anticipated

secular trends in adherence as a result of longitudinal followup, so models accommodated a background change in adherence prior to July 2011 and then permitted an immediate change in adherence in July 2011 as well as a change in trend over time thereafter. Models adjusted for cumulative time in study, and multiple observations from each participant were assumed to have an exchangeable correlation structure (chosen empirically). All models were assessed for confounding by a prespecified set of covariates: sex, age at enrollment, oral contraceptive use (male or no/yes; time-varying), self-reported sex with the primary study partner (none/any; time-varying), and antiretroviral therapy use by the HIV-seropositive partner (no/yes; time-varying). All analyses were performed using R version 3.1.0 (2014-04-10).

RESULTS

Each of the subsets analyzed was generally similar to the Partners PrEP Study as a whole (TABLE 1). The cohort of participants originally randomized to active PrEP was 37 percent female with an average age of 34 years at enrollment. The overwhelming majority were married and had, on average, four children. Participants in the MEMS cap substudy differed slightly from the full cohort in terms of sex, years of education, and income but were nevertheless similar in terms of baseline characteristics at the three sites using MEMS caps (Kabwohe, Kampala, and Tororo, Uganda). [19]

STUDY MEDICATION REFILL RATE Of the 3,163 participants randomized to active PrEP, 43 contributed no post-randomization followup at which medication refill could be assessed. The remaining 3,120 individuals contributed a total of 89,988 study months of followup to the analysis of refill rates, 64,898 before and 25,090 after July 2011. The odds of refilling declined slightly over time prior to 10 July 2011, at an adjusted background rate of 1.1 percent per month (95% confidence interval [CI], 0.28–1.8; $p = 0.01$). Immediately after 10 July 2011, there was a statistically significant improvement in refill activity, increasing from 97.2 to 97.4 percent (adjusted odds ratio [AOR], 1.24; 95% CI, 1.03–1.50; $p = 0.03$). Thereafter, the trend reversed, and the odds of refilling began to increase by 1.3 percent per month (95% CI, 0.86–3.6; $p_{\Delta} = 0.04$), climbing to 98.6 percent by July 2012 (FIGURE 1).

MONTHLY COUNT OF PILLS TAKEN Sixteen participants had no pill count data, so there were 3,104 participants available for the pill count analysis, contributing 58,442 study months of followup before and 22,246 after July 2011. Prior to July 2011, pill counts decreased by 0.0028 pills per month, but this trend was

not statistically significant ($p = 0.46$). After 10 July 2011, pill counts closely tracked refill activity. The average pill count immediately increased by 0.19 pills (95% CI, 0.015–0.36; $p = 0.03$) and by 0.018 more pills per month thereafter (95% CI, 0.001–0.036; $p_{\Delta} = 0.04$; FIGURE 2). A secondary analysis excluded months in which the participant was known to have run out of study medication (e.g., following a missed visit). This analysis included 3,098 participants, contributing 56,695 study months of followup before and 21,631 months after July 2011. Overall, pill counts were higher by this method, 26.9 versus 26.4. However, there was no significant shift in pill counts associated with the early release of positive trial results ($p = 0.95$), and secular trends were the same before and after July 2011 ($p_{\Delta} = 0.72$; FIGURE 2).

MONTHLY COUNT OF BOTTLE OPENINGS Of 745 participants originally randomized to active PrEP and enrolled into the MEMS cap substudy, 741 had MEMS cap data available for analysis, covering 7,564 study months of followup before and 6,345 months after July 2011. As with refill rates and pill counts, the monthly count of bottle openings decreased by an adjusted rate of 0.11 openings per month prior to July 2011 (95% CI, 0.072–0.14; $p < 0.01$). Thereafter, this rate did not change ($p_{\Delta} = 0.45$), nor did we observe any significant one-time shift in MEMS counts associated with the early release of trial results ($p = 0.71$; FIGURE 3).

TENOFOVIR DETECTION RATE Of the 200 participants originally randomized to active PrEP who were sampled for tenofovir testing, 197 had blood specimens available. In total, 1,233 samples were tested, 885 from before and 348 from after July 2011. The odds of detecting tenofovir in blood plasma decreased by an adjusted rate of 3.2 percent per month (95% CI, 1.5–4.8; $p < 0.01$) until 10 July 2011. After the early release of positive trial results, drug detection increased from 79.9 to 85.2 percent of samples, a 76 percent increase in odds (AOR, 1.76; 95% CI, 1.22–2.55; $p < 0.01$). However, the odds of detecting drug subsequently declined at an adjusted rate of 7.6 percent per month (95% CI, 3.9–11; $p_{\Delta} = 0.02$), and after twelve months of decline at this faster rate, the proportion of samples with detectable drug had effectively returned to the counterfactual level had efficacy not been demonstrated at an interim analysis (FIGURE 4).

ADHERENCE AMONG RE-RANDOMIZED PLACEBO ARM PARTICIPANTS Overall, participants who were randomized to placebo and chose to be re-randomized to active PrEP had higher refill rates, 97.9 versus 97.7 percent of visits (OR, 1.32; 95% CI, 1.09–1.61; $p < 0.01$). Monthly pill counts were also higher by 0.37 pills on average (95% CI, 0.18–0.55; $p < 0.01$), but there was no statistically significant difference in drug detection rates after July 2011 between those initially randomized to active PrEP and those re-randomized

from placebo (76.2 vs 71.4 percent of samples; $p = 0.60$).

SEXUAL BEHAVIOR AND ADHERENCE We found adherence, by all four measures, to be higher during months in which the participant reported having any sex with the primary, HIV-seropositive partner. The odds of refilling were 2.6 fold higher (95% CI, 2.2–3.2; $p < 0.01$) compared to months without sex with the HIV-seropositive partner. Monthly pill counts were higher by 1.2 pills (95% CI, 0.91–1.4; $p < 0.01$), and MEMS caps recorded an average of 1.5 more openings per month (95% CI, 0.97–2.1; $p < 0.01$). Drug detection rates were marginally higher, but the difference was not statistically significant (AOR, 1.1; 95% CI, 0.78–1.7; $p = 0.51$).

DISCUSSION

By all four measures, adherence in the Partners PrEP Study was relatively high. Study medication was dispensed at 96 percent of attended visits, and clinic-based pill counts indicated adherence levels of 97 percent.[1] On average, MEMS caps recorded bottle openings on 91 percent of days[19], and in this analysis PrEP drug was detected in 81 percent of plasma specimens collected at timepoints when the participant was expected to take study medication and had pills to take. All four measures declined marginally over time prior to the early release of trial results in July 2011, at which point there were statistically significant, albeit small and time-limited, improvements in adherence by some measures. These findings suggest that knowledge of PrEP efficacy is a motivator of adherence, although modest in the context of high background adherence in this trial population.

To date, four randomized, placebo-controlled clinical trials have demonstrated PrEP efficacy. However, two trials were stopped for futility, and it is believed that differential adherence was a key, contributing factor to these discrepant findings.[7, 8] Substantial effort has been made to characterize non-adherence in PrEP studies, and there is particular concern that in the context of a placebo-controlled trial, poor adherence could result from doubts regarding the product's efficacy or concerns about the potential of being randomized to placebo.[15] The Partners PrEP Study was uniquely poised to test for such an effect because the placebo-controlled study led directly into an open-label extension. The Partners PrEP Study followup after July 2011 resembles a real-world setting because all participants knew they were receiving a PrEP medication with proven benefit.

Prior research has established a negative correlation between adherence to daily medication and duration of use[23–27], and in this analysis we did observe a gradual decline in adherence over time prior to July 2011. However, after excluding months in which participants failed to refill their study medication, pill counts were relatively stable over time. This suggests that those participants who were motivated to refill their study medication were also generally motivated to adhere to the daily pill regimen, and those who were disinclined to take the medication tended not to refill at all. This is consistent with previous research that has shown that individuals tend to be persistent adherers or persistent non-adherers[20] and posits that refill initiative is a key mediator of high adherence in this study population. Therefore, it is encouraging that Partners PrEP Study refill rates were significantly and consistently higher after the early release of positive trial results and higher still among placebo arm participants who consented to extended followup on active PrEP.

However, pill counts tend to overestimate adherence, and electronic monitoring of pill bottles and plasma tenofovir levels were indicative of lower adherence than pill counts would suggest. Secular trends were different as well. Unlike refill rates and pill counts—which showed sustained improvement after July 2011, the background rate of decline in MEMS counts persisted throughout the open-label period, and increases in drug detection rates occurred then waned, returning to counterfactual levels within a year.

Importantly, we observed significantly lower objective measures of adherence in months when participants reported no sexual contact with the HIV-infected study partner compared to months during which sex occurred. This, in addition to the adherence improvements after July 2011, suggests that participants may have been making rational decisions regarding PrEP usage with regard to their current HIV risk and their understanding of PrEP efficacy.

Overall, the observed improvements in adherence associated with the early release of trial results are encouraging, but they should be interpreted within the limitations of this analysis. First, each adherence metric used in this study is imperfect in some way. Medication refill is only a crude proxy and clinic-based pill counts tend to overestimate adherence when unreturned pills are lost or intentionally ‘dumped’ prior to the visit. Testing for the presence of tenofovir in blood samples is potentially more objective, but it is still subject to participant manipulation (e.g., dosing just before scheduled visits) and may be modified by biologic or pharmacokinetic factors. Furthermore, the invasiveness of blood collection and high laboratory

costs make this impractical for frequent sampling across the entire Partners PrEP Study cohort. Thus, semiannual samples from 200 participants can give a general sense of adherence trends but may cloud more granular temporal patterns. Nevertheless, comparing multiple objective measures of adherence together can help to overcome the individual limitations of any single measure. Second, the discontinuation of the placebo arm and subsequent re-randomization required study sites to increase engagement in participant tracking and visit scheduling activities. To some degree, the observed improvements in adherence could be attributable this increased operational push rather than the self-motivation of the participants alone.

In conclusion, early release of positive trial results led to modest improvements in adherence to PrEP for prevention of HIV, against a background where adherence was already very high. There was a small but sustained improvement in refill activity and pill counts plus a large but short-lived increase in the odds of detecting tenofovir in blood plasma specimens. Participants who were originally randomized to the placebo arm and who opted to continue open-label followup, a subgroup self-selected by their desire to take active PrEP, were significantly more likely to refill their study medication and tended to have higher objective measures of adherence overall. Together, these results suggest that knowledge of PrEP efficacy was a motivator of adherence, even in this trial in which background levels of adherence were high. Continued study of PrEP adherence in delivery settings will be essential.

TABLE 1: Baseline characteristics of the full Partners PrEP Study cohort and adherence analysis subsets. Summaries are expressed as count (percent) or as mean (interquartile range).

	Subset				
	Partners PrEP Study	Active PrEP only	Placebo, then active PrEP	MEMS cap substudy	Sampled for TFV assay
Participants	4,747	3,163	1,264	1,146	300
Female	1,785 (38%)	1,164 (37%)	475 (38%)	539 (47%)	114 (38%)
Age	34 (28–40)	34 (28–40)	35 (29–40)	35 (30–40)	34 (28–39)
Married	4,677 (99%)	3,114 (98%)	1,250 (99%)	1,142 (> 99%)	291 (97%)
Number of children	4 (2–5)	4 (2–5)	4 (2–5)	4 (2–6)	4 (2–5)
Years of education	7 (4–10)	7 (4–10)	7 (4–10)	6 (3–7)	7 (5–10)
Any monthly income	3,770 (79%)	2,511 (79%)	1,023 (81%)	1,026 (90%)	230 (77%)

PrEP pre-exposure prophylaxis; MEMS medication event monitoring system; TFV tenofovir

	Before*	10 July 2011†	After*
OR (95% CI)‡	0.98 (0.98, 0.99)	1.20 (1.00, 1.44)	1.01 (0.99, 1.03)
p-value	$p < 0.001$	$p = 0.052$	$p_{\Delta} = 0.019$
AOR (95% CI)§	0.99 (0.98, 1.00)	1.24 (1.03, 1.50)	1.01 (0.99, 1.04)
p-value	$p = 0.008$	$p = 0.026$	$p_{\Delta} = 0.036$

months	-12	-6	0	6	12
n	2,520	2,829	2,712	2,088	1,173

* Odds ratio compares two consecutive months

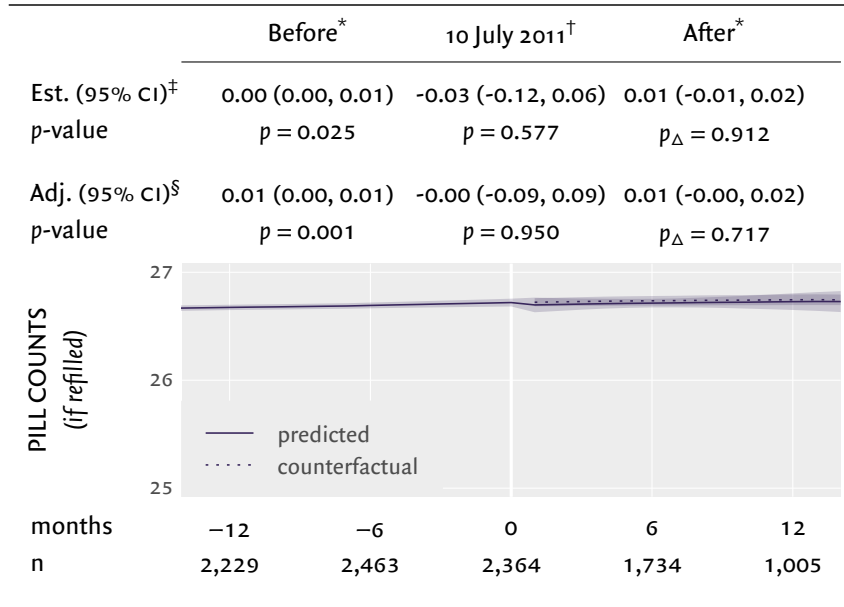
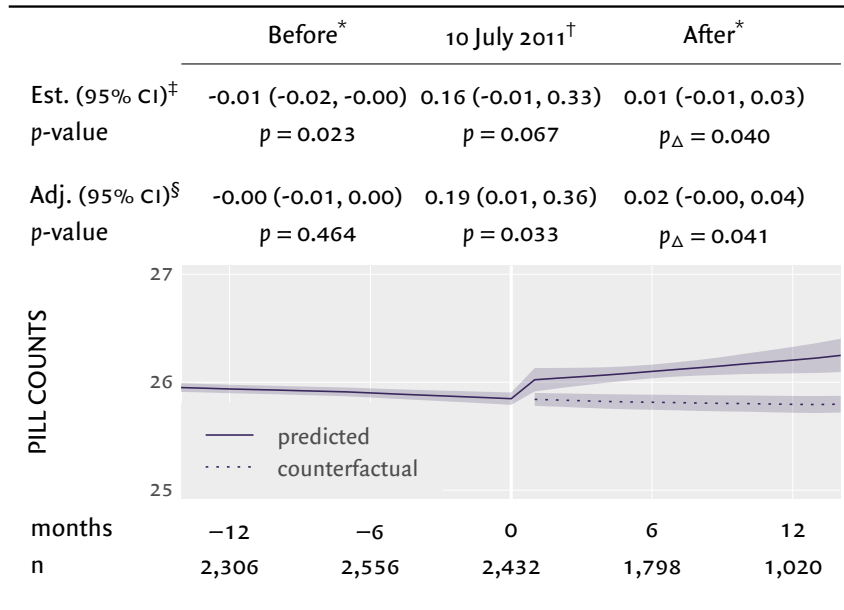
† Odds ratio describes a one-time change in refill rates

‡ odds ratio adjusted for cumulative time in study; plotted

§ odds ratio adjusted for cumulative time in study, sex, age, and self-reported sex with the primary study partner (none/any; time-varying)

p_{Δ} p-value against the null hypothesis that *before* and *after* odds ratios are the same

FIGURE 1: Predicted and counterfactual model estimates of study drug refill rates



* Estimate describes the per month change in average pill counts

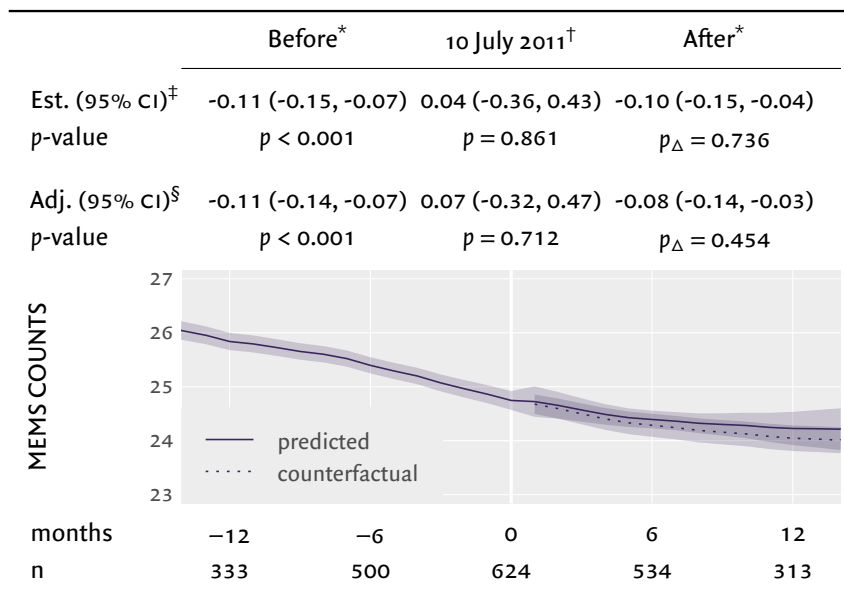
† Estimate describes a one-time change in average pill counts

‡ odds ratio adjusted for cumulative time in study; plotted

§ odds ratio adjusted for cumulative time in study, sex, age, and self-reported sex with the primary study partner (none/any; time-varying)

p_Δ p-value against the null hypothesis that *before* and *after* estimates are the same

FIGURE 2: Predicted and counterfactual model estimates of monthly pill counts



* Estimate describes the per month change in average MEMS counts

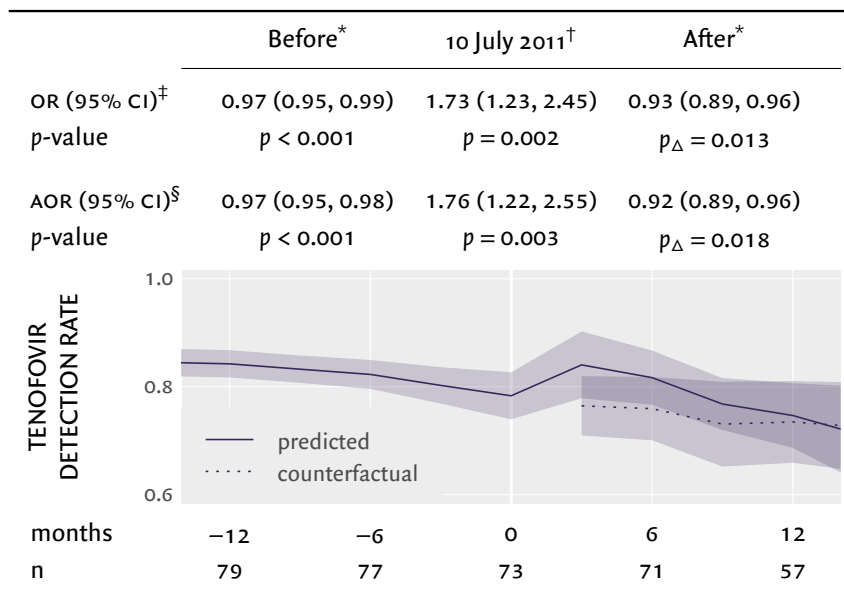
† Estimate describes a one-time change in average MEMS counts

‡ odds ratio adjusted for cumulative time in study; plotted

§ odds ratio adjusted for cumulative time in study, sex, age, and self-reported sex with the primary study partner (none/any; time-varying)

p_{Δ} p-value against the null hypothesis that *before* and *after* estimates are the same

FIGURE 3: Predicted and counterfactual model estimates of monthly MEMS counts



* Odds ratio compares two consecutive months

† Odds ratio describes a one-time change in drug detection rates

‡ odds ratio adjusted for cumulative time in study; plotted

§ odds ratio adjusted for cumulative time in study, sex, age, and self-reported sex with the primary study partner (none/any; time-varying)

p_{Δ} p-value against the null hypothesis that *before* and *after* odds ratios are the same

FIGURE 4: Predicted and counterfactual model estimates of tenofovir detection rates

REFERENCES

- [1] Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012 Aug;367(5):399–410.
- [2] Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013 Jun;381(9883):2083–90.
- [3] Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010 Dec;363(27):2587–2599.
- [4] Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012 Aug;367(5):423–34.
- [5] MARRAZZO JM, RAMJEE G, NAIR G, PALANEE T, MKHIZE B, NAKABIITO C, et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE Study (MTN 003). Paper presented at: CROI 2013. Proceedings of the 20th Conference on Retroviruses and Opportunistic Infections; 2013 Mar 3–6; Atlanta, GA.
- [6] Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2012 Aug;367(5):411–22.
- [7] Kashuba ADM, Patterson KB, Dumond JB, Cohen MS. Pre-exposure prophylaxis for HIV prevention: how to predict success. *Lancet*. 2012 Jun;379(9835):2409–11.
- [8] van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. *AIDS*. 2012 Apr;26(7):F13–9.
- [9] 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 Jul;17(6):2162–72.
- [10] Galea JT, Kinsler JJ, Salazar X, Lee SJ, Giron M, Sayles JN, et al. Acceptability of pre-exposure prophylaxis as an HIV prevention strategy: barriers and facilitators to pre-exposure prophylaxis uptake among at-risk Peruvian populations. *Int J STD AIDS*. 2011 May;22(5):256–62.
- [11] Mimiaga MJ, Case P, Johnson CV, Safren SA, Mayer KH. Preexposure antiretroviral prophylaxis attitudes in high-risk Boston area men who report having sex with men: limited knowledge and experience but potential for increased utilization after education. *J Acquir Immune Defic Syndr*. 2009 Jan;50(1):77–83.
- [12] Minnis AM, Gandham S, Richardson BA, Guddera V, Chen BA, Salata R, et al. Adherence and acceptability in MTN 001: a randomized cross-over trial of daily oral and topical tenofovir for HIV prevention in women. *AIDS Behav*. 2013 Feb;17(2):737–47.

- [13] Montgomery E, van der Straten A, Torjesen K. “Male involvement” in women and children’s HIV prevention: challenges in definition and interpretation. *J Acquir Immune Defic Syndr.* 2011 Aug;57(5):e114–6; author reply e116–7.
- [14] 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 Apr;7(4):e33103.
- [15] Tangmunkongvorakul A, Chariyalertsak S, Amico KR, Saokhieo P, Wannalak V, Sangangamsakun T, et al. Facilitators and barriers to medication adherence in an HIV prevention study among men who have sex with men in the iPrEx study in Chiang Mai, Thailand. *AIDS Care.* 2013 Aug;25(8):961–7.
- [16] Ware NC, Wyatt MA, Haberer JE, Baeten JM, Kintu A, Psaros C, et al. What’s love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. *J Acquir Immune Defic Syndr.* 2012 Apr;59(5):463–8.
- [17] Mujugira A, Baeten JM, Donnell D, Ndase P, Mugo NR, Barnes L, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention. *PLoS ONE.* 2011 Oct;6(10):e25828.
- [18] Ndase P, Celum C, Campbell J, Bukusi E, Kiarie J, Katabira E, et al. Successful discontinuation of the placebo arm and provision of an effective HIV prevention product after a positive interim efficacy result: the Partners PrEP study experience. *J Acquir Immune Defic Syndr.* 2014 Jun;66(2):206–12.
- [19] Haberer JE, Baeten JM, Campbell J, Wangisi J, Katabira E, Ronald A, et al. Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa. *PLoS Med.* 2013 Sep;10(9):e1001511.
- [20] Donnell D, Baeten JM, Bumpus NN, Brantley J, Bangsberg DR, Haberer JE, et al. HIV protective efficacy and correlates of tenofovir blood concentrations in a clinical trial of PrEP for HIV prevention. *JAIDS.* Forthcoming 2014.
- [21] Keller MJ, Madan RP, Torres NM, Fazzari MJ, Cho S, Kalyoussef S, et al. A randomized trial to assess anti-HIV activity in female genital tract secretions and soluble mucosal immunity following application of 1% tenofovir gel. *PLoS ONE.* 2011 Jan;6(1):e16475.
- [22] Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JE, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. *Sci Transl Med.* 2011 Dec;3(112):112re4.
- [23] Liu H, Miller LG, Hays RD, Golin CE, Wu T, Wenger NS, et al. Repeated measures longitudinal analyses of HIV virologic response as a function of percent adherence, dose timing, genotypic sensitivity, and other factors. *J Acquir Immune Defic Syndr.* 2006 Mar;41(3):315–22.
- [24] Mannheimer S, Friedland G, Matts J, Child C, Chesney M, Terry Bein Community Programs for Clinical Research on AIDS. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis.* 2002 Apr;34(8):1115–21.

- [25] Byakika-Tusiime J, Crane J, Oyugi JH, Ragland K, Kawuma A, Musoke P, et al. Longitudinal antiretroviral adherence in HIV+ Ugandan parents and their children initiating HAART in the MTCT-Plus family treatment model: role of depression in declining adherence over time. *AIDS Behav.* 2009 Jun;13 Suppl 1:82–91.
- [26] Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation.* 2009 Jun;119(23):3028–35.
- [27] Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med.* 2012 Sep;125(9):882–7.e1.