Title

Results from a Pre-exposure Prophylaxis Demonstration Project for At-risk Cisgender Women in the United States

Journal

Clinical Infectious Diseases, 73(7)

ISSN

1058-4838

Authors

Blumenthal, Jill

Jain, Sonia

He, Feng

et al.

Publication Date

2021-10-05

DOI

10.1093/cid/ciab328

Peer reviewed

Results from a PrEP Demonstration Project for At-Risk Cisgender Women in the United States

Jill Blumenthal MD MAS[1], Sonia Jain PhD[2], Feng He MS[2], K. Rivet Amico PhD[3], Ryan Kofron MS[4], Eric Ellorin MAS[1], Jamila K. Stockman PhD MPH[1], Christina Psaros[5], Gifty M. Ntim MD[4], Karen Chow[1], Peter L. Anderson PharmD[6], Richard Haubrich MD[7], Katya Corado MD[8], David J. Moore PhD[9], Sheldon Morris MD MPH[1], Raphael J. Landovitz MD MSc[4]

[1] Department of Medicine, University of California San Diego, San Diego, CA, USA
[2] Department of Family Medicine and Public Health, University of California San Diego, San Diego, CA, USA
[3] Department of Health Behavior and Health Education, School of Public Health, University of Michigan, Ann Arbor, MI, USA
[4] Department of Medicine, Ronald Reagan UCLA Medical Center, University of California Los Angeles, Los Angeles, CA, USA
[5] Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
[6] Department of Pharmaceutical Sciences, University of Colorado, Denver, CO, USA
[7] Gilead Sciences, Foster City, CA, USA
[8] Department of Medicine, Harbor-UCLA Medical Center, Torrance, CA, USA
[9] Department of Psychiatry, University of California San Diego, San Diego, CA, USA

Corresponding Author:
Jill Blumenthal
220 Dickinson Street Suite A
San Diego, CA 92103 USA
619-543-8080
jblumenthal@health.ucsd.edu

Summary: Cisgender women at risk for HIV were enrolled in a 48-week study of daily oral tenofovir disoproxil fumarate/emtricitabine. Overall, they had moderate adherence and low retention despite comprehensive adherence support. However, there were no incident HIV infections.

Abstract

Background: Daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is effective for reducing HIV acquisition among cisgender women. We report results from the first United States observational open-label demonstration project of PrEP among at-risk cisgender women.

Methods: Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGiS) was a 48-week single-arm open-label demonstration study of daily oral TDF/FTC in cisgender women ≥18 years old at-risk for HIV. Adherence was supported using two-way text messaging and titrated adherence counseling based on rapid-turnaround tenofovir diphosphate concentrations from dried blood spots. Study visits occurred at baseline, and at weeks 4, 12, and quarterly through week 48. Outcomes included TDF/FTC adherence, retention and persistence.

Results: From June 2016 to October 2018, 136 cisgender women enrolled [mean age 40 (SD 11); 38% non-Hispanic (NH) Black and 19% Latina]. At 48 weeks, 84 (62%) participants were retained and 62 (46%) remained on PrEP. Over one-third (12/31) of those on study but off PrEP throughout study discontinued TDF/FTC due to side effects, and one adverse event led to study discontinuation. Of 120 participants with drug concentrations measured, 67 (56%) had at least one concentration consistent with ≥6 doses/week (d/w); 22 (18%) had consistent ≥6 d/w across all study visits attended. There were no incident HIV infections and 4 incident bacterial STIs.

Conclusion: Adequate PrEP adherence for protective drug concentrations was not achieved for most study participants. More work needs to be done to fully explicate the reasons for non-adherence and low retention in cisgender women.

Keywords:
Pre-exposure prophylaxis, cisgender women, United States, adherence, retention

Background

Although the number of new HIV infections in the United States (US) has declined in the last decade, cisgender women account for 19% of all new HIV infections.[1] The incidence rate of HIV infections among cisgender women is highest in Black and Latina populations, who make up nearly 80% of the newly-diagnosed women.[1] The use of daily oral pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) has been shown to significantly reduce HIV incidence in cisgender women.[2,3] Despite these data, there has been limited research using TDF/FTC for HIV prevention among cisgender women in the US.[4] Although TDF/FTC PrEP has been approved in the US since 2012,[5] the majority of data on PrEP adherence in cisgender women comes from clinical trials in Sub-Saharan Africa with little known about women taking PrEP in the US. Recent data found that 95% of PrEP prescriptions in a large commercially insured population from 2012-2018 were for men.[6]

Adherence to PrEP among women remains an important topic. In the FEM-PrEP and VOICE studies[7,8], placebo-controlled randomized clinical trials (RCTs) of daily oral TDF-based PrEP in cisgender women, the majority of participants did not have detectable PrEP drug concentrations despite high self-reported adherence.[9] Interviews with FEM-PrEP participants who were non-adherent reported low HIV risk perception, fear of side effects and concern others might think they had HIV.[10] Adherence and retention in PrEP care among US women has not been well characterized. One PrEP RCT including US women showed high retention to study visits[11], but data suggest that sociodemographic and structural factors may make PrEP retention more challenging for cisgender women.[12] In a retrospective chart review of women taking PrEP through a community-based clinic in New York, retention in care at six months was ~40%.[13]

Given the challenges to maintain people on PrEP, clinical studies and implementation programs have included adherence support strategies using technology and behavioral interventions. One such intervention, Individualized Texting for Adherence Behavior (ITAB), an automated, personalized two-way text messaging system, is a low-cost

efficient method for increasing objective adherence of antiretrovirals (ARVs) among people living with HIV (PLWH)[14,15] and in MSM taking PrEP.[16] Additionally, point of care interventions delivered at PrEP dispensation visits including patient-centered counseling with rapid feedback of drug-level monitoring and problem solving have been used to improve PrEP use.[17] Using these tools adapted for the current study, we designed the first US demonstration project of oral PrEP among cisgender women at risk for HIV and report the primary results including PrEP adherence, retention and persistence.

Methods

Study Setting and Participants:

Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGiS) was a 48-week single-arm open-label PrEP demonstration study to estimate PrEP adherence, retention and persistence in HIV-negative cisgender women at risk for HIV taking once daily TDF/FTC. Participants were enrolled between June 2016 and October 2018 at five Southern California study sites, four in Los Angeles and one in San Diego.

Eligibility Criteria:

The study enrolled participants who were assigned female at birth and identified as female, aged ≥18 years, English- or Spanish-speaking, HIV-negative as assessed by fourth generation antigen/antibody or third generation antibody assay with HIV nucleic acid amplification test (NAAT) and creatinine clearance (CrCl) of ≥60 ml/min by the Cockcroft-Gault formula. Participants were at risk for acquiring HIV infection as defined by having: (1) condomless sex in the last 3 months with one or more male partners of unknown HIV status, with the partner known to be at substantial risk of HIV infection (e.g., injects drugs; bisexual; exchanges sex for money, goods or services; recently incarcerated; from a region with HIV prevalence >1%, intimate partner violence); (2) STI (rectal or vaginal gonorrhea, rectal chlamydia or syphilis) in the last 6 months; (3) post-exposure prophylaxis use during the last

12 months; (4) ≥1 HIV-infected sexual partner for >4 weeks; or (5) sex in exchange for money, goods or services. Participants were excluded if they had active hepatitis B, 2+ or higher proteinuria or signs or symptoms of primary HIV infection. Initially, patients were excluded from participation if they had a positive urine pregnancy test at screening. In May 2017, data were sufficiently robust supporting the use of TDF/FTC as PrEP during pregnancy that an amendment was approved removing the exclusion for pregnancy at study entry.

Study Procedures:

Study visits occurred at baseline, week 4, week 12, then quarterly through week 48 with a follow-up telephone call at week 60. An adequate supply of TDF/FTC was provided to all participants at no cost at baseline and weeks 4, 12, 24 and 36. A self-administered computer assisted survey instrument was used to assess baseline demographics and HIV risk factors as well as longitudinal assessments of HIV risk and medication use behavior. Safety testing including CrCl, pregnancy and HIV (Abbott Architect) were performed at baseline, week 4, week 12, then quarterly through week 48. Asymptomatic STI testing was performed at baseline and every six months and included syphilis (serum rapid plasma reagin and, if positive, confirmatory treponemal test) and NAAT of urine and swabs of pharynx and rectum for chlamydia and gonorrhea (Hologic Aptima), with more frequest testing if symptomatic.

Adherence was supported with a multimodal approach using two-way text messaging (ITAB)[16] and titrated adherence counseling using Integrated Next Step Counseling (iNSC) followed by Lifesteps for PrEP (also referred to as PrEP-Steps[17]), for participants with ongoing adherence challenges, based on rapid-turnaround tenofovir diphosphate (TFV-DP) concentrations through the Colorado Antiviral Pharmacology laboratory at the University of Colorado.[17] See Appendix I for details of the adherence intervention.

Study Design:

Participants received iNSC from the study coordinator at their baseline visit and at all subsequent visits attended. Suboptimal prespecified adherence concentrations (TFV-DP levels of <1050 fmol/punch, corresponding to <6-7 daily doses/week over the past 1-2 months) triggered "targeted iNSC," implemented when drug levels were received by the site 14 days after the clinic visit.[18] Participants in this sub-optimal range were contacted by the study coordinator within 7-14 days of receipt, informed of their results with "targeted iNSC" support deployed by telephone or in person. If the result was a repeat sub-optimal level, the study coordinator scheduled the participant for the first of 4 (+2 booster) Lifesteps for PrEP sessions. (See Figure 1).

Study Measures:

Primary study outcomes included PrEP adherence, retention and persistence. Adherence was assessed by quantifying intraerythrocytic TFV-DP concentrations in dried blood spots at all follow-up study visits during which the participant reported any TDF/FTC use. TFV-DP was measured using a validated liquid chromatography–tandem mass spectrometry assay.[19,20] TFV-DP concentrations of ≥1050 fmol/punch were considered protective, indicating ≥6 doses on average per week over the prior 1-2 months at steady state. This threshold was higher than the protective level of 700 fmol/punch in MSM due to the notion that women require higher adherence than MSM because of lower vaginal versus rectal drug distribution.[21] The week 4 TFV-DP concentration was adjusted for non-steady state pharmacokinetics assuming a 17-day half-life.[19] Post-hoc, we examined TFV-DP concentrations of ≥700 fmol/punch, suggestive of ≥4 doses on average per week.[22] Self-reported PrEP adherence was assessed as the proportion of participants responding affirmatively to daily iTAB text prompts indicating dose ingestion over all days prior to the last study visit. PrEP retention was assessed as the proportion of participants who attended each study visit over participants expected. PrEP persistence was assessed as the proportion of participants who attended each study visit on study drug, as defined by patients reporting

they were currently taking PrEP, over participants expected. Additional measures assessed at baseline and follow-up visits included sexual behaviors (number and types of partners, sexual acts), depressive symptoms through the Patient Health Questionnaire-9 (PHQ-9)[23], substance use through Alcohol Use Disorders Identification Test (AUDIT)[24] and Drug Abuse Screening Test (DAST-10)[25], intimate partner violence (IPV) (history of physical, sexual or emotional abuse in the last year), interest in becoming pregnant in the next 6 months and HIV literacy (HIV Knowledge Questionnaire–18).[26]

Statistical Analysis:

Patient demographics and baseline characteristics were reported with summary statistics including means (SD) for continuous variables, medians (IQRs) for count variables and frequencies for categorical variables. Wilcoxon rank sum was used to compare the proportion of affirmative iTAB responses over all days prior to the last study visit with TFV-DP drug concentrations at each study visit. Adverse events were summarized by grade using the Division of AIDS (DAIDS) Table.[27] We calculated HIV and STI incidence rates and confidence intervals using the total number of new HIV infections or STIs divided by person-years at risk during the observation period. Statistical software R (version 3.6.1) was used for the analysis (http://www.r-project.org).

Ethical Considerations

The research protocol was approved by the relevant Institutional Review Boards at each participating site or institution. The study was registered at clinicaltrials.gov (NCT02584140).

Results

Study Population and Baseline Demographics

Of 167 participants completing a screening visit, 136 cisgender women met the study eligibility criteria and completed a baseline visit. No participants were newly diagnosed with HIV at study enrollment (see Figure 2). A total of 136 participants were enrolled with a mean

age of 40 years (SD 11); 38% were Non-Hispanic Black, 22% Non-Hispanic White, 19% Latina and 21% other race/ethnicity. The median number of sex partners in the last 3 months was 1 (IQR 1-3), and 12 participants (9%) were diagnosed with an STI at baseline (see Table 1).

PrEP Adherence

The adherence threshold of ≥6 doses/week was achieved at each visit by 54/117 (46%) participants on PrEP at week 4, 45/102 (44%) at week 12, 29/80 (36%) at week 24, 28/69 (41%) at week 36 and 25/66 (38%) at week 48, with 25/136 (18%) for the total cohort at week 48 (see Figure 3). Of 120 participants with TFV-DP concentrations measured, 67 (56%) had at least one measurement consistent with ≥6 doses/week and 22 (18%) had TFV-DP concentrations consistent with ≥6 doses/week at available study visits attended. Approximately two-thirds of participants had drug concentrations consistent with ≥4 doses/week, with 84/117 (72%) at week 4, 62/102 (61%) at week 12, 54/80 (68%) at week 24, 45/69 (65%) at week 36 and 42/66 (64%) at week 48 (see Figure 3). Of 120 participants with TFV-DP concentrations measured, 90 (75%) had at least one measurement consistent with ≥4 dose/week and 53 (44%) had TFV-DP concentrations consistent with ≥4 dose/week across available study visits attended. For each study visit (e.g., 30-day for week 4 visit and 90-day look back for all other visits), participants with concentrations consistent with ≥6 doses/week had a higher proportion of affirmative iTAB responses compared to those with concentrations consistent with <6 doses/week (see Table 2). Findings were similar using the ≥4 dose/week cut-off except they were not statistically significant at week 24 (data not shown).

Retention and Persistence

PrEP retention by visit was 121/136 (89%) at week 4, 110/136 (81%) at week 12, 98/136 (72%) at week 24, 84/136 (62%) at both weeks 36 and 48. Fifty-two (38%) participants did not complete the week 48 visit. Of these 52 participants, 15 (29%) requested to withdraw with only 1 participant citing side effects. The remaining 37 (71%) of the 52 participants who

did not complete the week 48 visit were lost to follow-up, with non-retention information only available for two participants. Thirty-one participants discontinued study drug between weeks 4-48, but remained on study, with nearly half (n=14) citing concerns about side effects or taking pills. At week 48, 62 (46%) reported that they were taking study drug. Of 65 participants who completed the week 60 telephone visit, n=36 remained on TDF/FTC by linking to external PrEP services. Of 26 reporting reasons for not continuing on PrEP, one-third (n=9) were concerned about side effects or taking pills, 6 had not seen a doctor or lacked insurance and 5 did not feel they were at risk (see Table 3). Of the 57 participants citing reasons for non-persistence at any study visit, 2 reported becoming pregnant as the reason for discontinuing TDF/FTC.

Adverse Events, Pregnancy, STI and HIV Incidence

Seventy-two (53%) participants experienced a total of 164 grade 2-3 adverse events, of which 126 were grade 2-3 decreases in CrCl in 61 unique participants. There were no grade 4 adverse events reported. Of the 37 grade 2-3 non-renal events, 8 were determined to be study related and 2 were unknown if study-related (see Table 4). Over the course of the study, there were 7 pregnancies in 7 participants, with 5 carried to term, 1 spontaneous and 1 elective abortion. The STI incidence rate was 5 /100 person-years (95% CI 2-10), representing six infections including 1 syphilis, 2 gonorrhea and 3 non-vaginal chlamydia infections. No incident HIV infections were detected, yielding an HIV incidence rate of 0 /100 person-years (95% CI 0-0.027).

Discussion

We deployed daily oral TDF/FTC among cisgender women considered at-risk for HIV acquisition using expanded CDC-based criteria and used iTAB and titrated adherence counseling to optimize adherence and retention, both interventions which had showed promising effects among MSM.[16,17] We found a decline in adherence concentrations over

time and high loss to follow-up, despite a comprehensive protocol to support participant adherence to PrEP, based primarily around feedback if TFV-DP levels were consistent with taking fewer than 6 doses per week as well as daily iTAB adherence promotion text messages.

While this strict protocol was intended to support participants, there may have been both positive and negative consequences. A study of highly adherent individuals by MEMS caps (i.e. those with ≧6 doses per week) who received feedback that they did not have protective drug levels felt discouraged, resulting in them discontinuing study drug or stopping the study all together.[28] On the other hand, there was a strong association between iTAB responses and drug concentrations, suggesting that those with high self-reported adherence were indeed taking their PrEP, and monitoring drug levels may not be needed in addition to adherence supports such as text messages or other reminder systems. In addition, over 75% of participants at week 48 reported that the text messaging intervention was helpful for adherence and would recommend that PrEP users be provided with drug level feedback (see Appendix II), suggesting that this combination intervention was highly acceptable to many participants.

PrEP retention worsened over time, analogous to what has been seen in real world settings,[29,30] despite great effort to retain study participants. This finding may reflect the social demographics and risk factors of the women in our study who had high rates of IPV, depression and substance use. More work needs to be done to further elucidate additional predictors of adherence and retention. Studies have shown that women and individuals of color have been shown to be less likely retained in PrEP care.[31] Given that nearly half of our participants were in serodiscordant relationships and most had one reported male sexual partner, women may have stopped PrEP and study visits as a result of low objective or perceived risk for HIV acquisition. However, having only one male sex partner may actually be an important predictor of HIV acquisition suggesting partner behavior contributes most to risk.[32]

Despite prior hypothetical concerns for increased side effects with TDF/FTC in women as compared to men due to pharmacokinetic differences[33], there were fewer side effects than anticipated. However, concerns about possible side effects was the most commonly reported reason for drug discontinuation. Although there were no differences seen in renal dysfunction[34,35] or fracture incidence[3] among cisgender women using PrEP versus placebo in PrEP trials that included cisgender women, the better-known and -publicized data regarding toxicities of TDF/FTC in PLWH may have been more accessible to study participants. Alternative PrEP agents including tenofovir alafenomide (TAF)/FTC and long-acting cabotegravir with safer side effect profiles may be more appealing to cisgender women seeking biomedical strategies for HIV prevention, although TAF is still under investigation for women.

We found low HIV and STI incidence rates, similar to previous PrEP studies including cisgender women in the US.[11] One potential reason for the low rates seen is the overall older age of our study partipants, with young age being one of the most consistent predictors of bacterial STI acquisition.[36] While no study participant acquired HIV while on study, it is difficult to determine if PrEP prevented HIV or if the study population was in fact at low risk for infection, despite study criteria to include individuals at "high risk" for HIV. Still, compared to MSM taking PrEP, populations of women at risk for HIV may not necessarily have high STI rates or numbers of sex partners.[37] In addition, low STI rates may actually serve as a barrier to adherence and retention as STI acquisition is often linked to HIV transmission.

Strengths of this study include enrolling a diverse cohort with many of the risks associated with HIV acquisition and using a comprehensive adherence intervention with rapid drug level feedback. There are also several limitations to this work. First, the sample is small, and thus it may not be generalizable to other US women at risk for HIV taking PrEP. While the study was not a randomized clinical trial, it was also not a real world study as routine PrEP care, medication refills and drug level feedback were provided as part of the study and thus insurance coverage or prescriptions refill costs were not barriers to adherence or retention. As with many PrEP studies, behavior is self-reported and is subject

to recall and desirability bias. Finally, we have no information on participants who were lost to follow-up, leaving a large gap in understanding why individuals did not continue on study and discontinued study product.

Although we found that cisgender women in a US PrEP demonstration project had lower adherence and retention than seen previously in studies involving MSM, a direct comparison should not be made given the multitude of barriers faced by women to participating in HIV research and clinical care, particularly stigma and medical mistrust.[38-40] It is imperative that PrEP be available to everyone at risk for HIV including women. Cisgender women need better resources to help them understand their risk for acquiring HIV and make informed decisions about PrEP use. Future research should focus on barriers to HIV prevention in order to optimize adherence and retention in cisgender women.

Acknowledgements: The authors would like to thank and acknowledge the study participants for their time and contributions to this research.

Sources of Support: This work was supported by the California HIV/AIDS Research Program (CHRP) grants EI11-SD-005B and E111-LA-002B; and the UCLA Center for AIDS Research (CFAR) grant 5P30AI028697. Dr. Blumenthal's research was supported by the NIH Grant KL2TR001444 of CTSA funding. Dr. Stockman acknowledges support from the San Diego Center for AIDS Research (Grant #P30AI036214).

Potential Conflicts of Interest: K.R.A. reports grants and personal fees from Gilead Sciences, outside the submitted work. R.H. is an employee and stock holder of Gilead Sciences. S.M. reports stock in Bristol Meyers Squibb, Pfizer, and Geron; and grant support to institution from Gilead and Merck, outside the submitted work. K.C. reports grants from Gilead, outside the submitted work. R.L. reports scientific advisory board fees from Gilead Sciences and Merck; honoraria from Roche and Janssen; and non-financial support from Gilead Sciences, outside the submitted work. C.P. reports consulting fees from Brown University and UNC, outside the submitted work. All other authors have no potential conflicts

References

1. CDC. HIV and Women, 2020.
2. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *The New England journal of medicine* 2012; **367**(5): 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**(5): 423-34.
4. Bailey JL, Molino ST, Vega AD, Badowski M. A Review of HIV Pre-Exposure Prophylaxis: The Female Perspective. *Infect Dis Ther* 2017; **6**(3): 363-82.
5. FDA. https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM312290.pdf. 2012 (accessed May 25 2018).
6. Song HJ, Squires P, Wilson D, Lo-Ciganic WH, Cook RL, Park H. Trends in HIV Preexposure Prophylaxis Prescribing in the United States, 2012-2018. *Jama* 2020; **324**(4): 395-7.
7. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012; **367**(5): 411-22.
8. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015; **372**(6): 509-18.
9. Corneli A, Wang M, Agot K, et al. Perception of HIV risk and adherence to a daily, investigational pill for HIV prevention in FEM-PrEP. *J Acquir Immune Defic Syndr* 2014; **67**(5): 555-63.
10. Corneli A, Perry B, McKenna K, et al. Participants' Explanations for Nonadherence in the FEM-PrEP Clinical Trial. *J Acquir Immune Defic Syndr* 2016; **71**(4): 452-61.
11. Gulick RM, Wilkin TJ, Chen YQ, et al. Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV Infection in Women: A Phase 2 Randomized Trial. *Annals of internal medicine* 2017; **167**(6): 384-93.
12. Magazi B, Stadler J, Delany-Moretlwe S, et al. Influences on visit retention in clinical trials: insights from qualitative research during the VOICE trial in Johannesburg, South Africa. *BMC women's health* 2014; **14**: 88.
13. Blackstock OJ, Patel VV, Felsen U, Park C, Jain S. Pre-exposure prophylaxis prescribing and retention in care among heterosexual women at a community-based comprehensive sexual health clinic. *AIDS care* 2017; **29**(7): 866-9.
14. Moore DJ, Montoya JL, Blackstone K, et al. Preliminary Evidence for Feasibility, Use, and Acceptability of Individualized Texting for Adherence Building for Antiretroviral Adherence and Substance Use Assessment among HIV-Infected Methamphetamine Users. *AIDS research and treatment* 2013; **2013**: 585143.
15. Moore DJ, Poquette A, Casaletto KB, et al. Individualized Texting for Adherence Building (iTAB): Improving Antiretroviral Dose Timing Among HIV-Infected Persons with Co-occurring Bipolar Disorder. *AIDS Behav* 2015; **19**(3): 459-71.
16. Moore DJ, Jain S, Dube MP, et al. Randomized Controlled Trial of Daily Text Messages To Support Adherence to PrEP In At-Risk for HIV Individuals: The TAPIR Study. *Clin Infect Dis* 2017.
17. Landovitz RJ, Beymer M, Kofron R, et al. Plasma Tenofovir Levels to Support Adherence to TDF/FTC Preexposure Prophylaxis for HIV Prevention in MSM in Los Angeles, California. *Journal of acquired immune deficiency syndromes (1999)* 2017; **76**(5): 501-11.

18. R. Amico K, McMahan V, Goicochea P, et al. Supporting Study Product Use and Accuracy in Self-Report in the iPrEx Study: Next Step Counseling and Neutral Assessment. *AIDS and Behavior* 2012; **16**(5): 1243-59.
19. Castillo-Mancilla JR, Zheng JH, Rower JE, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses* 2013; **29**(2): 384-90.
20. Zheng JH, Rower C, McAllister K, et al. Application of an intracellular assay for determination of tenofovir-diphosphate and emtricitabine-triphosphate from erythrocytes using dried blood spots. *Journal of pharmaceutical and biomedical analysis* 2016; **122**: 16-20.
21. Cottrell ML, Yang KH, Prince HM, et al. A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine. *J Infect Dis* 2016.
22. Anderson PL, Liu AY, Castillo-Mancilla JR, et al. Intracellular Tenofovir-Diphosphate and Emtricitabine-Triphosphate in Dried Blood Spots following Directly Observed Therapy. *Antimicrob Agents Chemother* 2018; **62**(1).
23. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine* 2001; **16**(9): 606-13.
24. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction* 1993; **88**(6): 791-804.
25. Skinner HA. The Drug Abuse Screening Test. . *Addictive Behaviors* 1982; **7**: 363-71.
26. Carey MP, Schroder KE. Development and psychometric evaluation of the brief HIV Knowledge Questionnaire. *AIDS education and prevention : official publication of the International Society for AIDS Education* 2002; **14**(2): 172-82.
27. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017.
28. Pyra M, Anderson P, Haberer JE, et al. Tenofovir-Diphosphate as a Marker of HIV Pre-exposure Prophylaxis Use Among East African Men and Women. *Front Pharmacol* 2019; **10**: 401.
29. Chan PA, Mena L, Patel R, et al. Retention in care outcomes for HIV pre-exposure prophylaxis implementation programmes among men who have sex with men in three US cities. *Journal of the International AIDS Society* 2016; **19**(1): 20903.
30. Hojilla JC, Vlahov D, Crouch PC, Dawson-Rose C, Freeborn K, Carrico A. HIV Pre-exposure Prophylaxis (PrEP) Uptake and Retention Among Men Who Have Sex with Men in a Community-Based Sexual Health Clinic. *AIDS Behav* 2018; **22**(4): 1096-9.
31. Marcus JL, Hurley LB, Hare CB, et al. Preexposure Prophylaxis for HIV Prevention in a Large Integrated Health Care System: Adherence, Renal Safety, and Discontinuation. *J Acquir Immune Defic Syndr* 2016; **73**(5): 540-6.
32. Harawa NT, McCuller WJ, Chavers C, Janson M. HIV risk behaviors among Black/African American and Hispanic/Latina Female partners of men who have sex with men and women. *AIDS Behav* 2013; **17**(3): 848-55.
33. Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol Sex Differ* 2020; **11**(1): 32.
34. Mugwanya KK, Wyatt C, Celum C, et al. Changes in glomerular kidney function among HIV-1-uninfected men and women receiving emtricitabine-tenofovir disoproxil

fumarate preexposure prophylaxis: a randomized clinical trial. *JAMA internal medicine* 2015; **175**(2): 246-54.
35. Mandala J, Nanda K, Wang M, et al. Liver and renal safety of tenofovir disoproxil fumarate in combination with emtricitabine among African women in a pre-exposure prophylaxis trial. *BMC Pharmacol Toxicol* 2014; **15**: 77.
36. CDC. STD Surveillance Report, 2017.
37. Calabrese SK, Willie TC, Galvao RW, et al. Current US Guidelines for Prescribing HIV Pre-exposure Prophylaxis (PrEP) Disqualify Many Women Who Are at Risk and Motivated to Use PrEP. *J Acquir Immune Defic Syndr* 2019; **81**(4): 395-405.
38. Grewe ME, Ma Y, Gilbertson A, Rennie S, Tucker JD. Women in HIV cure research: multilevel interventions to improve sex equity in recruitment. *J Virus Erad* 2016; **2**: 49-51.
39. Johnson M, Samarina A, Xi H, et al. Barriers to access to care reported by women living with HIV across 27 countries. *AIDS care* 2015; **27**(10): 1220-30.
40. Randolph SD, Golin C, Welgus H, Lightfoot AF, Harding CJ, Riggins LF. How Perceived Structural Racism and Discrimination and Medical Mistrust in the Health System Influences Participation in HIV Health Services for Black Women Living in the United States South: A Qualitative, Descriptive Study. *The Journal of the Association of Nurses in AIDS Care : JANAC* 2020; **31**(5): 598-605.

Table 1: Baseline Sociodemographics and Risk Factors (n=136)

	Enrolled n=136
Age mean years (SD)	40 (11)
Weight in pounds mean (SD)	186 (58)
Race/Ethnicity	
Non-Hispanic White	30 (22%)
Non-Hispanic Black	52 (38%)
Latina	26 (19%)
Other	28 (21%)
Education – ≤ High School	61 (45%)
Income – < $2000 per month (n=109)	74 (68%)
Employment – Unemployed/Unable to work (n=128)	60 (47%)
Relationship status – single/open (n=133)	63 (47%)
HIV risk group	
HIV+ partner	64 (47%)
Exchange sex	21 (15%)
Partner with unknown HIV status at risk for HIV	51 (38%)
Study site	
UCSD AntiViral Research Center	40 (29%)
AIDS Project Los Angeles	50 (37%)
To Help Everyone Los Angeles	34 (25%)
Harbor UCLA	7 (5%)
University of Southern California	5 (4%)
Number sex partners last 3 mo median (IQR)	1 (1-3)
Participants with STI diagnosed at baseline* – positive (n=134)	12 (9%)
PHQ-9 – moderate/severe depression (n=124)	24 (19%)
AUDIT – moderate/high risk (n=125)	16 (13%)
DAST – severe/substantial risk (n=124)	13 (10%)
Intimate Partner Violence last year – yes to any (n=123)	56 (46%)
Pregnancy Interest – yes (n=123)	31 (25%)
KQ18 HIV Knowledge mean (SD)	13 (4)

*STI diagnosed at baseline included: rectal chlamydia (1), cervical chlamydia (2), pharyngeal chlamydia (1), rectal gonorrhea (3), cervical gonorrhea (3), pharyngeal gonorrhea (2), syphilis (7)

Table 2: iTAB Adherence

Study Visit	N	TFV-DP concentration (fmol/punch)	Proportion affirmative iTAB responses*, mean (SD)	P-value
Week 4	58	<1050	0.49 (0.40)	<0.001
	50	≥1050	0.80 (0.32)	
Week 12	55	<1050	0.53 (0.38)	0.005
	44	≥1050	0.76 (0.31)	
Week 24	49	<1050	0.61 (0.34)	0.029
	28	≥1050	0.77 (0.27)	
Week 36	39	<1050	0.49 (0.40)	0.008
	27	≥1050	0.78 (0.25)	
Week 48	38	<1050	0.47 (0.39)	0.03
	24	≥1050	0.71 (0.32)	

*Proportion of affirmative iTAB responses is the percentage of "yes" responses to daily iTAB adherence queries over the total number of queries sent prior to the study visit

Table 3: Reasons for Non-Persistence

Reasons not on PrEP	**Week 4-48 (n=31)**	**Week 60 (n=26)**
Worry about side effects/long-term effects	14	6
Don't want to take pills	0	3
Don't feel like it works	2	0
Can't stick with taking it	3	0
Not having sex/not at risk	1	4
Monogamous	2	1
Medical issues	3	1
Have not seen doctor	0	2
Lack of insurance	0	4
Became pregnant	1	1
Stolen/Worry might get stolen	2	1
Other	3	3

Table 4: Adverse Events

	Total	Decrease in CrCl*	Study-related (or possibly)†
Total Grade 2+ AEs	164	126	10
Grade 2	150	118	10
Grade 3	14	8	0
Grade 4	0	0	0
Number of participants who experienced at least one AE	72	-	-

*Grade 2 AEs for CrCl are determined by result of <90 to 60 ml/min or 10% to <30% decrease from sscreening/baseline. Grade 3 AEs for CrCl are determined by result of <60 to 30 ml/min or 30 to <50% decrease from screening/baseline.

†Two unknown if study-related

Abbreviations: AE; adverse events, CrCl; creatinine clearance

FIGURE LEGENDS

Figure 1: Intervention Worklfow

Figure 2: Study Consort

Figure 3: TDF/FTC Adherence by Study Visit, n=136

Figure 1: Intervention Workflow

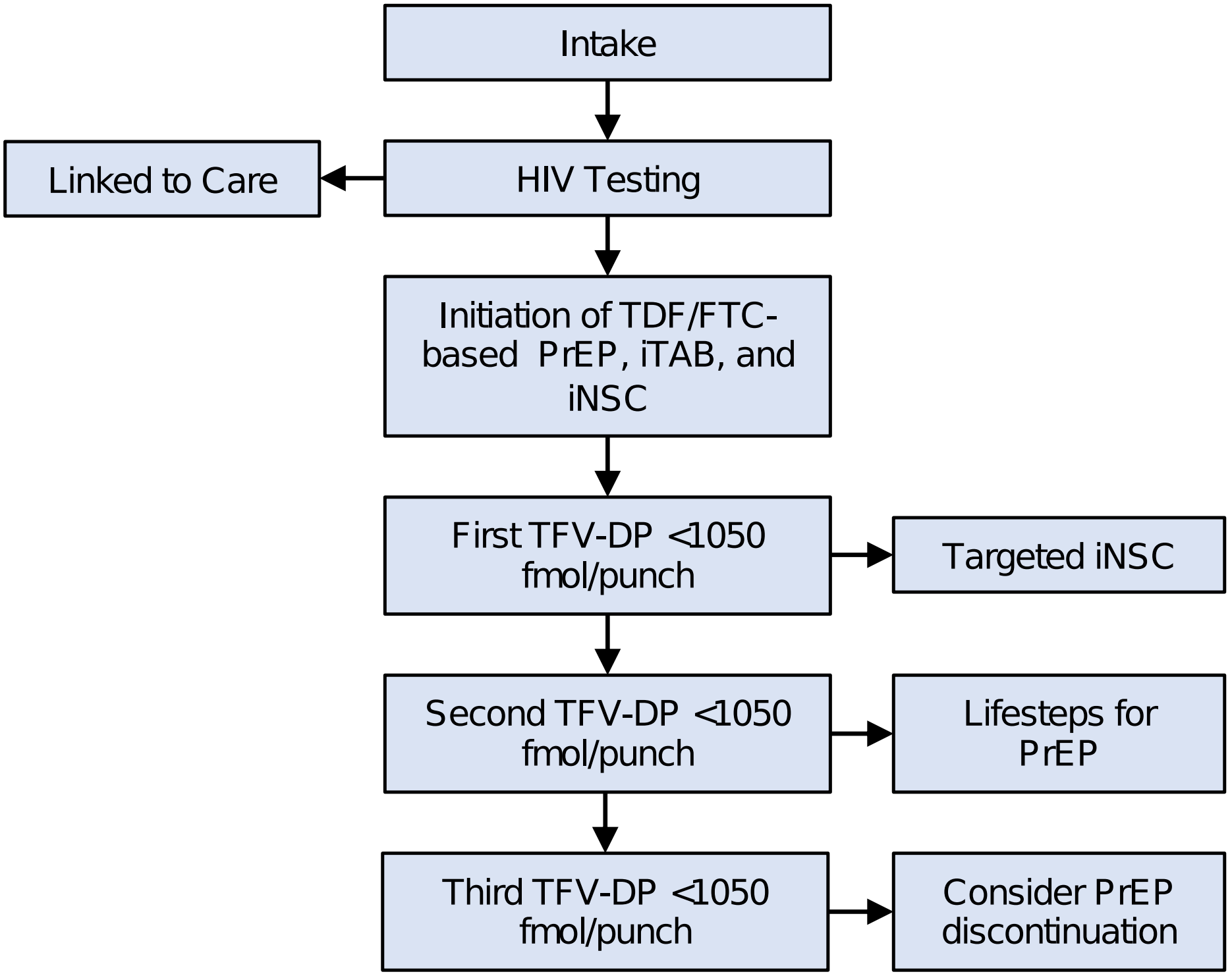


Figure 2: Study Consort

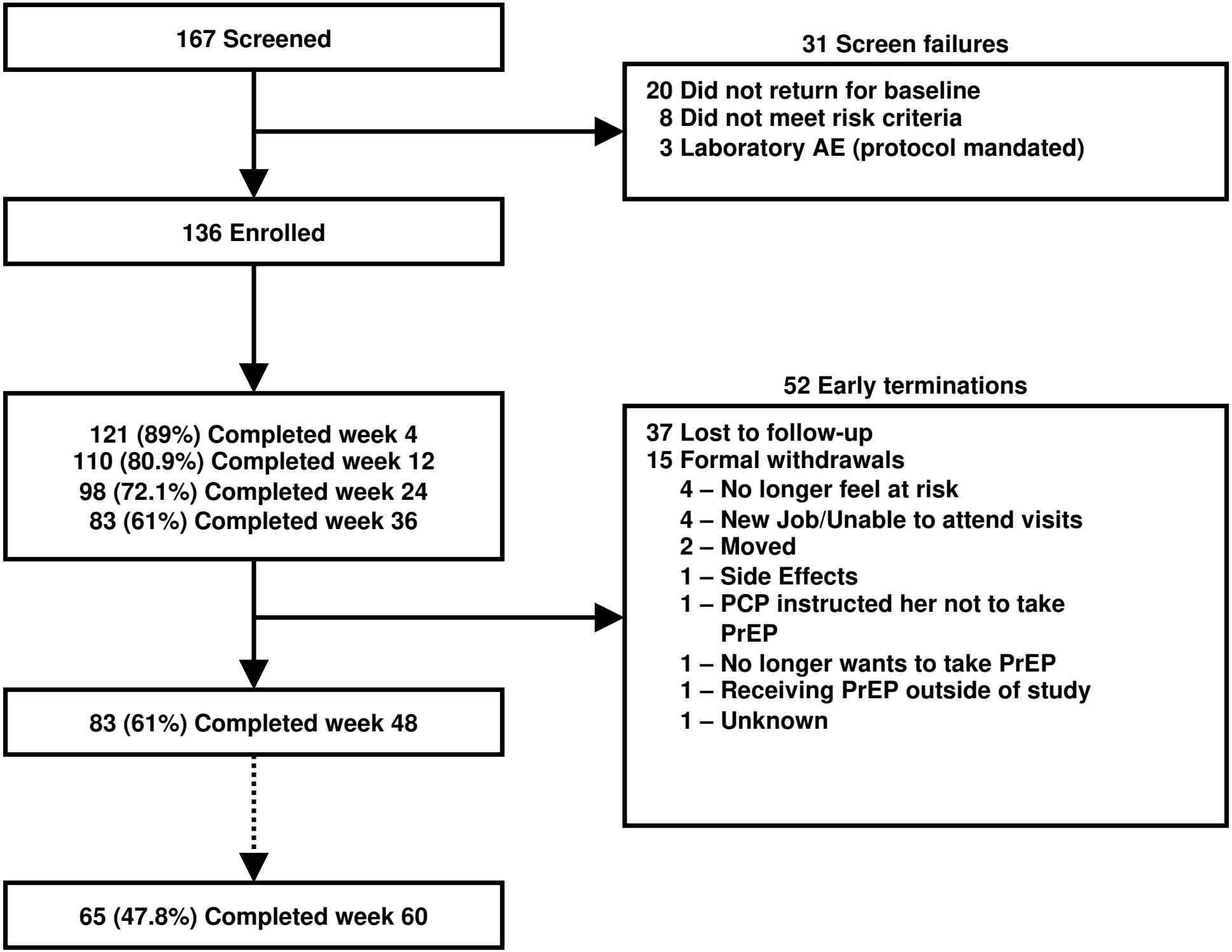
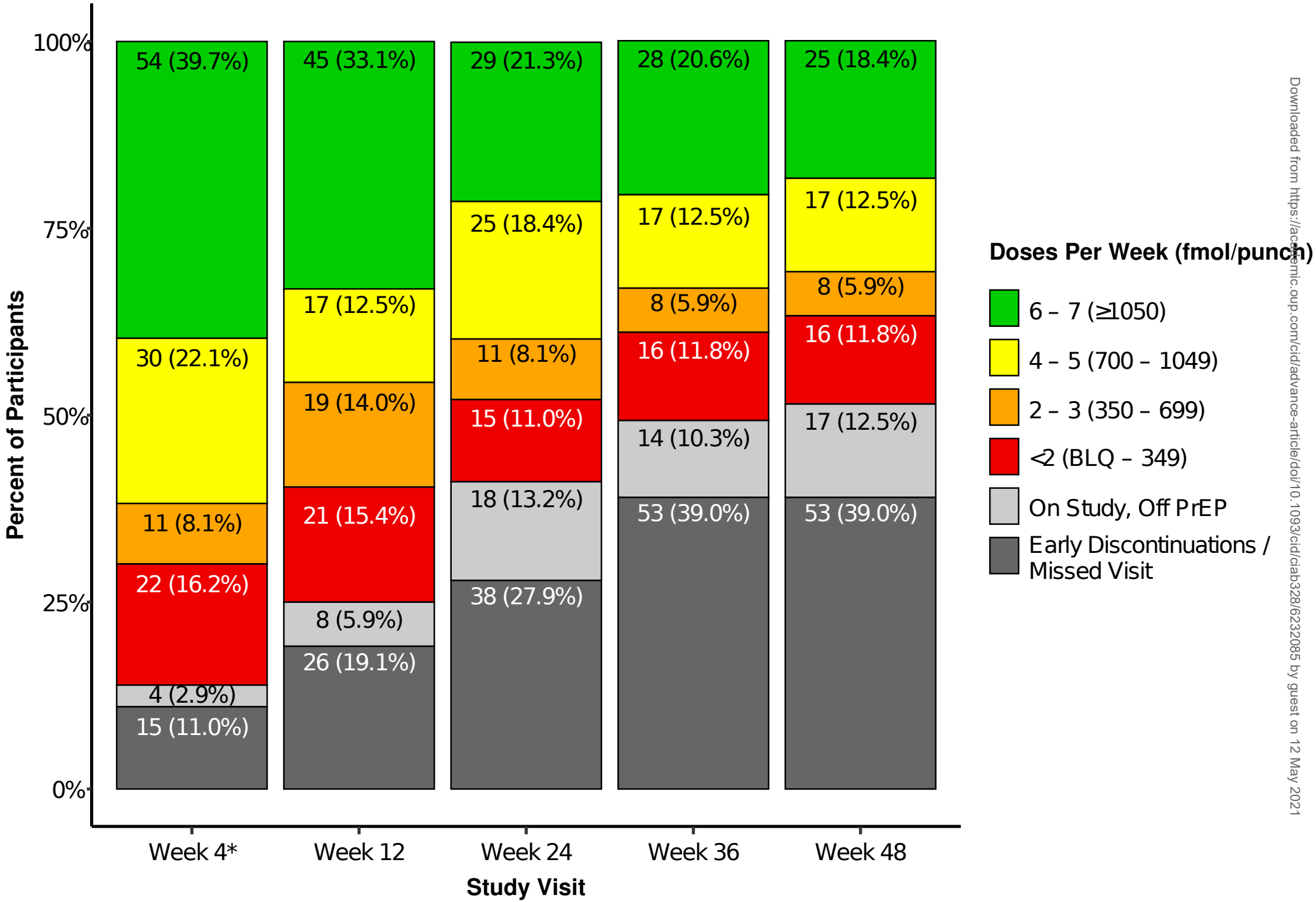


Figure 3: TDF/FTC Adherence by Study Visit, n=136



* Category values for Week 4 adjusted for days on therapy, as steady state not yet achieved