# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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**Table of Contents**

**Table of Figures**



**Table of Tables**

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## 2.0 Reviewing ethical committees and regulatory bodies

### A. United States

- Protection of Human Subjects Committee, FHI 360
- US Food and Drug Administration

### B. Belgium

- Universitair Ziekenhuis Antwerpen Ethisch Comité

### C. Kenya

- Kenyatta National Hospital/University of Nairobi Ethics and Research Committee
- Republic of Kenya Ministry of Health Pharmacy & Poisons Board

### D. Tanzania

- Kilimanjaro Christian Medical Center Research Ethics Committee
- National Institute for Medical Research (NIMR)
- London School of Hygiene and Tropical Medicine Ethics Committee
- Tanzania Food and Drugs Authority

### E. South Africa

- Medunsa Campus Research and Ethics Committee
- University of the Free State Ethics Committee
- Medicines Control Council

## 3.0 Protocol amendments after trial implementation and rationale

### A. Protocol version 2.0

- **Removal of bone density sub-study**: Since the approval of protocol version 1.0, multiple studies evaluating TDF/FTC for pre-exposure prophylaxis (PrEP) for HIV prevention were begun which included assessing bone mineral density as an endpoint. Due to the few number of FEM-PrEP study sites with access to DEXA scans, it was unlikely that FEM-PrEP would have sufficient statistical power to identify a meaningful association between TDF/FTC use and bone mineral density.

- **Removal of Hepatitis B antibody testing after vaccine series completion:** Antibody testing after vaccine series completion was not warranted because vaccine administration

guidelines do not recommend Hepatitis B antibody testing after vaccination among the general population.

- **Addition of a week 60 visit:** Because the impact of TDF/FTC on HIV antibody production is unknown (i.e., it is theoretically possible that TDF/FTC could suppress viral replication and therefore delay antibody production after initial infection), an additional visit at week 60 (i.e., 8-weeks after permanent product withdrawal) was added to ensure that all incident HIV infections are detected.

- **Removal of mandatory PCR testing on all final visit samples:** In protocol version 1.0, PCR testing was conducted on all final visits samples due to the concern that TDF/FTC may suppress viral replication and therefore delay antibody production and subsequent antibody detection. However, with the addition of HIV testing at a week 60 visit (see above), PCR testing on all final visit samples was no longer necessary.

- **HIV algorithm change to serial testing**: Parallel HIV testing was included in protocol v1.0 solely due to former legal requirements in some countries (i.e, an individual could not have been provided an HIV diagnosis based on the results of one testing algorithm). Since approval of protocol v1.0, this restriction was lifted and parallel testing allowed.

- **Changes in retesting and product interruption requirements for some toxicity values**: Instructions for toxicity management were clarified. Expert guidance from investigators of other PrEP trials and from a nephrologist was incorporated.

- **Addition of HIV resistance and TDF/FTC drug level testing on first HIV-positive PCR sample among seroconverters**: To meet secondary objectives #1 and #2 of the protocol, it was deemed critical to know drug levels and resistance information as close to the time of infection as possible.

- **Addition of Hepatitis B antigen testing at time of product interruption among participants who were Hepatitis B antibody negative at baseline who refused/did not complete vaccination series:** To identify all participants who may have been at risk of a Hepatitis B flare; this was an additional measure to protect the safety of participants.

- **Addition of chemistry testing at any follow-up visit subsequent to any product restart following toxicity-related interruption:** To rapidly identify any participant who developed toxicity after study product restart.

### B. Following the January 2011 IDMC meeting

The IDMC recommended an immediate study product withdrawal for every grade 3 AST/ALT toxicity at the January 2011 meeting. Therefore all grade 3 AST/ALT levels were from 19Jan2011 onward reported as “possibly/probably/definitively study drug-related” which led to immediate study product interruption (before toxicity confirmation) per protocol.

## 4.0 Eligibility criteria

To be eligible for inclusion in this study, at screening the participant must have been:

- Willing and able (see criterion 2) to provide written informed consent to be screened for and to participate in the trial
- Able to answer a percentage of informed consent screening (75%) and enrollment (100%) comprehension quiz questions correctly
- Between 18-35 years old , inclusive
- At higher risk of becoming HIV infected, defined as 1) has had at least one vaginal sex act in the last two weeks, or 2) has had more than one sexual partner in the last month
- Have a final negative result according to the site-specific screening HIV testing algorithm and a final negative result at enrollment according to the study HIV testing algorithm
- Willing to participate in all aspects of the study and to comply with study procedures, for up to 60 weeks, including:
    - Be randomized
    - Use study product as directed
    - Adhere to follow-up schedule and willing to be contacted by site staff between study visits (by phone and/or in person)
    - Use a study-approved effective non-barrier method of contraception for the duration of the study
    - Take study product, as evidenced by swallowing a vitamin tablet that is similar in size to the study product at enrollment
    - Provide contact information and agree to some form of contact method throughout the study
- Not intending to relocate out of the area for the duration of the study participation and does not have a job or other obligations that may require long absences from the area (>1 month at a time)
- In general good health and have no condition (social or medical) which, in the opinion of the Site Investigator, would make study participation unsafe or complicate data interpretation
- Not pregnant or breastfeeding, and does not anticipate a desire for pregnancy during the 52 weeks of on-product participation
- Medically eligible at screening including:
    - Adequate renal function (serum creatinine <1.5 mg/dl and creatinine clearance ≥ 60mL/min estimated by the Cockcroft-Gault Creatinine Clearance Formula(74)
    - Adequate hepatic function (hepatic transaminases ALT and AST <2x upper limit of normal [ULN] [according to local normal ranges])
    - HBsAg negative
    - Serum phosphorus levels above the lower limit of the normal range (according to local normal ranges – grade 3 & 4 hypophosphatemia will be excluded even if within normal local ranges)
- Not received or receiving an experimental HIV vaccine, participating in another HIV prevention study or participating in any other clinical trial with a biomedical intervention
- No clinical signs of liver disease (e.g., ascites, spider angiomata, hepatomegaly, jaundice)
- No definite evidence of glycosuria or proteinuria (i.e., no repeated positive (≥+1) urine dipstick). If a urine dipstick is positive for either glucose and/or protein at the first test, a second urine sample will be tested

- No history of pathological bone fractures
- No history of adverse reaction to latex
- Not taking any of the following medications:
    - Nephrotoxic agents
        - aminoglycoside antibiotics (including gentamicin)
        - IV amphotericin B
        - cidofovir
        - cisplatin
        - foscarnet
        - IV pentamidine
        - oral or IV vancomycin
        - oral or IV gancyclovir
        - other agents with significant nephrotoxic potential
    - Drugs that slow renal excretion
        - Probenecid
        - Immune system modulators
        - Systemic chemotherapeutic agents (i.e. cancer treatment medications)
        - Systemic corticosteroids
        - Interleukin-2 (IL-2)
        - Immunomodulators
        - Interferon (alpha, beta, or gamma)
        - Other antiretrovirals (including nucleoside analogs, non-nucleoside reverse transcriptase inhibitors, protease inhibitors or investigational antiretroviral agents)

If a prospective participant was taking any prohibited medications at screening, she could have been considered for enrollment if she stopped the product immediately after screening to allow wash out prior to enrollment.

All Hepatitis B surface antigen negative participants were tested for Hepatitis B antibody and were offered vaccination, independent of whether they were enrolled in the trial.

# 5.0 Endpoint definitions

### A. Primary endpoints

1. Combined incidence of HIV-1 and HIV-2 infection as determined by detection of HIV antibodies using HIV rapid tests. For participants who seroconvert, HIV RNA-PCR will be done on the previous visit(s) sample(s) to assess whether the participant was truly HIV-1 uninfected at her previous visit(s), including RNA-PCR testing on the week 52 sample if the week 56 sample is antibody positive. Whenever the RNA-PCR test is negative, DNA-PCR will be performed. If a participant tests positive on or prior to week 52 using the RNA-PCR, DNA-PCR and/or the rapid test algorithm, then she will be considered positive for the primary analysis. All endpoints will be confirmed by the ITM. Participants with estimated infection dates after week 52 will only be included in secondary analyses;

A central laboratory at the Institute of Tropical Medicine (Antwerp, Belgium) confirmed HIV antibody results on stored plasma samples. Quantitative HIV-1 RNA polymerase-chain-reaction (PCR) and DNA PCR testing on plasma and upper layer packed cells (ULPC) specimens, respectively, was used to refine the infection window and to identify participants who were in the seronegative window period of acute infection at enrollment.

2. Incidence of confirmed Grade 2 or higher serum creatinine toxicity, and Grade 3 or higher AST, ALT, or phosphorus toxicity during and 4 weeks after study product administration; and

3. Frequency and nature of adverse events (AEs) during and within 4 weeks after study product administration.

**B. Secondary endpoints**

1. HIV-1 viral load and CD4+ T cell counts (when sample is available) at the earliest time of HIV detection (RNA PCR or DNA PCR), at HIV seroconversion (i.e., first detection of antibodies) and at 4, 8, 12, 16, 24, 36 and 52 weeks after seroconversion diagnosis.

2. FTC and/or tenofovir resistance at the earliest time of HIV detection (RNA PCR or DNA PCR), HIV seroconversion (i.e., first detection of antibodies), and 4 weeks after seroconversion diagnosis. If resistance is present, testing will be repeated at weeks 12, 24, 36 and 52 post-HIV diagnosis as necessary (resistance testing will stop after the first visit in which no resistance is detected);

3. Incidence of pregnancy loss, prematurity, low birth weight, and major and minor congenital abnormalities;

4. Pill counts and participant report of adherence to once-daily pill taking;

5. Participant report of the number of sexual partners and frequency of unprotected sexual acts over time; and

6. Participant report of sexual behaviors and sex partner characteristics by participants who seroconvert and HIV negative participants.

## 6.0 Analysis populations

1. **Screened population** (N=4163): all women who signed a screening informed consent

2. **Randomized population** (N=2120): all women who signed an enrollment informed consent and were randomized in the trial

3. **Primary effectiveness population** (N=2056): subset of the randomized population, excluding women who were HIV antibody negative but PCR positive at enrollment (N=2) and women

with no HIV follow-up data (N=62). Women in this population were censored at week 52, seroconversion, or the first visit after 18 April 2011, whichever came first.

4. **Primary safety population** (N=2058): also a subset of the randomized population, excluding two women who returned all their study pills unused and 60 women with no follow-up data. Women who were HIV antibody negative but PCR positive at enrollment were not excluded.

5. **Secondary effectiveness population** (N=2056): subset of the safety population which excludes women who were HIV antibody negative but PCR positive at enrollment. Unlike for the primary effectiveness and safety populations, time in analysis is censored 30 days after the last product distribution or at the visit of permanent product withdrawal, and one woman who received the wrong drug at enrollment is analyzed according to drug received.

## 7.0 Statistical methods (additional information)

An independent data monitoring committee (IDMC) reviewed interim data after approximately 25%, 50%, and 75% of the HIV infections were observed. At the final planned interim analysis the IDMC was asked for guidance on whether the trial should stop for futility, as per protocol and the IDMC Operational Plan.

Time of HIV infection was estimated as the midpoint of each seroconverter's infection window: the last visit without evidence of infection and the first visit with evidence of infection according to PCR testing. Participants without a post-randomization HIV test and seroconverters determined to be HIV PCR positive at enrollment were excluded from the primary analysis. Time contributed to the primary analysis by seronegative participants was censored at the earlier of either week 52 or the visit when product was withdrawn following closure of the trial.

Primary safety analyses were based on log-rank tests of no difference in times to detection of Grade 2 or higher serum creatinine toxicity and Grade 3 or higher AST, ALT, or phosphorus toxicities. Other AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 12) and summarized in frequency tables, with exact p-values for tests of no differences in proportions of participants experiencing events.

A pill coverage rate was computed for each participant based on the number of pills distributed minus the number returned relative to the number of days contributed to the primary analysis, with 80% coverage chosen as a pre-specified cut-off for covariate and subgroup analyses. Adherence was also summarized according to participant self-report. Risk disinhibition was assessed based on change in reported condom use, coital frequency and numbers of partners during the trial. Differences in CD4+ count and logged viral load were summarized using descriptive t-tests.

## 8.0 Case-control analysis of plasma drug levels

Cases included each participant assigned TDF/FTC who became infected with HIV after enrollment but before the earlier of week 52 or the first visit after 18APR2011. For each case,

three controls were randomly selected from the TDF/FTC group, matched on site and timing of the infection window (one case had no matched controls selected, but remained analyzable due to overlapping strata with another case-control set). To be eligible as a control for a particular case, a participant must have completed scheduled visits corresponding to the infection window; if the case infection window was based on one or more unscheduled visits, then the nearest scheduled visit was used when determining eligible controls. Cases could serve as controls during the time they were uninfected, and controls could be matched to more than one case.

Conditional logistic regression was used to compute descriptive p-values for differences between cases and controls in the rate of TFV plasma drug concentration ≥ 10 ng/ml, controlling for effects of age ≥25 years, use of injectable contraception, and one or more sex acts without a condom in the 28 days prior to the start of the infection window.

## 9.0 Interim Analysis

The IDMC convened for a final interim review on April 7, 2011, at which time the database included 28 HIV infections in each arm (crude rate ratio (RR), 0.99; 95% CI, 0.56 - 1.73). The committee drew attention to a higher pregnancy rate among women assigned TDF/FTC (incidence rate (IR), 11.8/100 woman-years vs. 6.4/100 woman-years; crude RR, 1.85; 95% CI, 1.20 - 2.90), but had no specific concerns about AEs or study quality indicators. The decision to stop the trial due to the lack of effectiveness was made on April 14, 2011, and product was withdrawn from each participant still in active follow-up at their first visit after April 18, 2011.

## 10.0 Recruitment

FEM-PrEP researchers adapted the PLACE Method (an innovative method originally developed to improve the reach of AIDS-prevention programs) to help develop FEM-PrEP's recruitment strategy.

During trial preparation at most sites, researchers interviewed members of the general community to identify the most common establishments (such as taverns and guest houses) where people meet potential sexual partners. They then conducted interviews with managers and owners, male patrons, female patrons, and employees of these establishments to learn more about the establishments and the people who socialize there.

Using these data, as well as staff experience from conducting the preparedness research, geographical areas of higher risk were identified and prioritized for recruitment. A global positioning system (GPS) unit was used to log the coordinates of the recruitment establishments and place them on maps using a geographic information system (GIS). This also allowed for the grouping of higher-risk areas, and helped to prioritize the recruitment process at some sites.

During the implementation of FEM-PrEP, the study's staff members systematically recruited potential participants, starting with the areas that were prioritized during the preparedness research. The staff recruited from one or two priority areas at a time, focusing initially on the establishments that were identified from the interview data. They also recruited from other

places in the priority areas such as voluntary counseling and testing centers, from clinics that treat sexually transmitted infections, and other establishments. Each month strategic decisions were made on where to recruit next, based on the staff's experience with the recruitment activities and a review of the screening and recruitment data.

## 11.0 Visit procedure details

Enrollment occurred 2-4 weeks after the screening visit. Blood plasma and upper layer packed cells (ULPC) were stored at enrollment and each follow-up visit for future HIV and drug concentration testing. Hepatic and renal function was assessed at weeks 4, 12, 24, 36, 52, 56 and when clinically indicated. A questionnaire on sexual behaviors was administered at screening, enrollment, and weeks 12, 24, 36, 52, and 56. Self-reported study product adherence was assessed through a face-to-face interview at each 4-week visit until product was withdrawn. The adherence assessment was conducted prior to adherence counseling and was done by staff who did not provide the counseling.

Study pharmacists gave participants uniquely numbered bottles containing 30 tablets of their randomly assigned product at enrollment and each follow-up visit through week 48, and trained counselors facilitated participant-centered and goal-oriented counseling at each visit. Participants were counseled to take one pill around the same time every day with or without food, asked to return bottles and unused drug at each visit, and offered a choice of adherence tools.

A gynecological examination with sexually transmitted infection (STI) testing was done at screening and at the final visit on product, or whenever clinically indicated. Treatable STIs, diagnosed via laboratory procedures or by syndromic approach, were treated free of charge.

Women who had a positive pregnancy test during follow-up were taken off product until they were no longer pregnant or breastfeeding. Product use was also temporarily interrupted or withdrawn due to protocol-defined chemistry abnormalities. If a participant missed a visit, she was not re-supplied with study product until her next visit upon the condition she had a negative HIV and pregnancy test. Participants who did not HIV seroconvert continued to receive monthly HIV testing, regardless of product withdrawal. Women who seroconverted were taken off study product, followed for an additional 52 weeks, and referred for care.

## 12.0 Management of chemistry abnormalities

Participants were asked to inform the study staff of any medical problems while they were taking part in the study. AEs were identified during laboratory testing, medical history interviews and physical examinations. Treatment for AEs possibly/probably/definitely related to study participation was provided by the study clinic, to the extent possible, at no cost to the participant. When treatment was required beyond the capacity of the study clinic, the study doctors referred the participant to appropriate services or organizations that could provide care, and for which payment by the participant may have been required. In the case of referral, site staff requested the participant's oral consent to obtain medical records related to the AE; the consent wasdocumented in her clinic notes.

All clinical and laboratory toxicities weremanaged according to standard medical guidelines. Detailed instructions for the management of liver, kidney and phosphorus abnormalities are given below (sections 10.1.5.1-10.1.5.3). Grade 3 and 4 laboratory abnormalities that are (possibly, probably or definitely) related to study drug and all bone fractures will be reported to FHI within 24 hours.

Participants with clinical or laboratory toxicities that require interruption or withdrawal of the study drug were followed at weekly intervals as much as possible, with additional testing when deemed clinically appropriate, until the toxicity resolved or stabilized. Whenever the study drug was restarted after a liver or renal toxicity occurred, the chemistry test was repeated at the participant's next follow-up visit. Participants who had study product interrupted or withdrawn were encouraged to remain in the study. When the study product was permanently withdrawn due to a toxicity, the chemistry test was stopped once the levels returned to baseline or stabilized.

**A. Hepatic toxicity management**

*Grade 1* (ALT/AST 1.25-2.5 x ULN): study drug was continued at the discretion of the site investigator. Hepatic function tests were repeated at the next scheduled study visit.

*Grade 2* (ALT/AST 2.6-5.0 x ULN): Study drug use could continue but the toxicity had to be confirmed by repeat testing of an additional collected specimen, preferably within seven calendar days. If the toxicity was confirmed, there were two options:

- The site clinician considered the toxicity (probably) unrelated to the study drug, study drug may have been continued and hepatic function tests were repeated at the next scheduled study visit.
- If the site clinician considered the toxicity (possibly/probably/definitely) related to the study drug, the study drug was interrupted upon confirmation. AST/ALT levels were monitored weekly, if possible, until resolution to ≤ Grade 1 when study drug could be restarted. If levels did not decrease to ≤ Grade 1, study drug was not restarted and testing stopped when the levels stabilized.

*Grade 3* (ALT/AST 5.1-10.0 x ULN):

- If the site clinician considered the toxicity (probably) *unrelated* to the study drug, study drug could be continued. Toxicity was confirmed by repeat testing of an additional collected specimen, preferably within seven calendar days. If the toxicity was confirmed, the study drug was interrupted and AST/ALT levels were monitored weekly, if possible, until resolution to ≤ Grade 1 when study drug could be restarted. If levels did not decrease to ≤ Grade 1, study drug was not restarted and testing stopped when the levels stabilized.
- If the site clinician considered the toxicity (*possibly/probably/definitely) study drug related*, the study drug was interrupted immediately (before confirmation). AST/ALT levels were monitored weekly, if possible, until resolution to ≤ Grade 1 when study drug could be restarted. If levels did not decrease to ≤ Grade 1, study drug was not restarted and testing stopped when the levels stabilized.

*Grade 4* (ALT/AST >10.0 x ULN): study drug was interrupted immediately. If confirmed and

- If the site clinician considered the toxicity (probably) *unrelated* to the study drug, the AST/ALT levels were monitored weekly, if possible, until resolution to ≤ Grade 1 when study drug could be restarted. If the Grade 4 toxicity recurred, the study drug was permanently withdrawn. If levels did not decrease to ≤ Grade 1, study drug was not restarted and testing stopped when the levels stabilized.
- If the site clinician considered the toxicity (*possibly/probably/definitely) study drug related*, the study drug was permanently withdrawn and AST/ALT levels testing done until resolution to ≤ Grade 1 or stabilization.

**B. Serum creatinine management**

*Grade 1* (an increase in creatinine >1.5 x above baseline for women with a baseline creatinine of ≤1.0 mg/dl **or** creatinine of 1.1-1.3 x ULN): Toxicity was confirmed by repeat testing of an additional specimen, preferably within seven calendar days. If result was confirmed, study drug was temporarily interrupted. Levels were monitored weekly, if possible, until creatinine returns to < Grade 1 and <1.3X above baseline, when study drug could be restarted. If the levels did not return to < Grade 1 and <1.3X above baseline, study drug was not restarted and testing stopped when the levels stabilized.

*Grade 2* (1.4-1.8 x ULN): Study drug was interrupted immediately. Toxicity was confirmed by repeat testing of an additional specimen, preferably within seven calendar days. If confirmed,

- If the site clinician considered the toxicity (probably) *unrelated* to the study drug, the kidney function was monitored weekly, if possible, until creatinine is < Grade 1and < 1.3X baseline when study drug could be restarted. If levels did not decrease to < Grade 1 and <1.3X above baseline, study drug was not restarted and testing stopped when the levels stabilized.
- If the site clinician considered the toxicity (*possibly/probably/definitely) study drug related*, the study drug was permanently withdrawn and the kidney function was followed until resolution to < Grade 1 and <1.3X baseline or stabilization.

*Grade 3* (1.9-3.4 x ULN) or *Grade 4* (≥3.5 x ULN) or calculated creatinine clearance <50mL/min: Study drug was interrupted immediately. Toxicity was confirmed by repeat testing of an additional specimen, preferably within seven calendar days. If confirmed study drug was permanently withdrawn (independent of relationship to study drug). Creatinine levels were monitored until resolution to < Grade 1 and < 1.3X above baseline or stabilization.

**C. Hypophosphatemia management**

*Grade 1*: The DAIDS AE Grading Table defines Grade 1 phosphorus abnormalities as from 2.5 mg/dl (lower value) to the lower limit of normal (upper value). For the purposes of this study, the lower limit of normal for phosphorus was defined as 2.5 mg/dl. Thus, there will be no Grade 1 phosphorus abnormalities defined for this study.

*Grade 2* (2.0-2.4 mg/dL): there were two possibilities dependent on the creatinine, creatinine clearance and urine dipstick results:

- If creatinine as well as creatinine clearance were *normal* and the urine analysis did not show new glycosuria (≥+1) or new proteinuria (≥+2), the study drug could be continued. The participant was advised to increase intake of food rich in phosphate (see study manual for details). At the following monthly visit phosphate, creatinine, creatinine clearance, bicarbonate, and urine analysis were performed. If the hypophosphatemia was associated with a decreased bicarbonate level (CO2 ≤17 mEq/l) or if any of the other tests have become abnormal, the study drug was permanently withdrawn and the kidney function monitored until resolution or stabilization.
- If the Grade 2 hypophosphatemia was immediately associated with *abnormal* creatinine/creatinine clearance or an abnormal urine dipstick result, the study product was immediately and permanently withdrawn (thus without/before bicarbonate level assessment) and the kidney function monitored until resolution or stabilization.

*Grade 3* (1.0-1.9 mg/dL) or *Grade 4* (< 1.00 mg/dL): there were two possibilities dependent on the creatinine, creatinine clearance and urine dipstick results:

- If creatinine as well as creatinine clearance were *normal* and the urine analysis did not show new glycosuria (≥+1) or new proteinuria (≥+2), the study drug could be continued. The participant was advised to increase intake of food rich in phosphate (see study manual for details). Within 7 days, phosphate, creatinine, creatinine clearance, bicarbonate, and urine analysis were performed. If the hypophosphatemia was associated with a decreased bicarbonate level (CO2 ≤17 mEq/l) or if any of the other tests have become abnormal, the study drug was permanently withdrawn and the kidney function monitored until resolution or stabilization.
- If the hypophosphatemia was immediately associated with *abnormal* creatinine/creatinine clearance or an abnormal urine dipstick result, the study product was immediately and permanently withdrawn (thus without/before bicarbonate level assessment) and the kidney function monitored until resolution or stabilization.
- Hyperphosphatemia was reported as an AE but not considered of clinical relevance.

## 13.0 Randomization, allocation concealment and blinding procedures

Participants were randomized to one of eight blinded letter groups (four corresponding to TDF/FTC and four to placebo) in equal ratios using a randomly permuted block design, stratified on site. Allocation groups were concealed in sequentially numbered opaque envelopes that were consecutively assigned at enrollment. Only pharmacists and study monitors knew which blinded letter group each participant was assigned, but they did not know which groups corresponded to TDF/FTC.

The FEM-PrEP trial implemented multiple procedures to ensure the blind was maintained during the trial. Placebo tablets matched TDF/FTC tablets in size, color, and taste. Each bottle of study drug was labeled with a unique five-digit number corresponding to one of the eight randomization letters (A-H). Only the pharmacist at each study site had access to the list linking bottle numbers to randomization letter. This multi-layered blinding procedure was chosen to minimize the likelihood that clinical staff members, through knowledge of a participant's letter group, could link participant reported adverse events with a particular letter group. In addition, pharmacists were only allowed access to participant records necessary to dispense study drug

(i.e., they did not have access to full participant files containing clinical study notes and adverse event forms) for the same rationale nor were they involved adherence counseling (pharmacists strictly provided pill taking instructions). Lastly, study drug and non-study medications were dispensed by separate pharmacists.

## 14.0 Adherence counseling

An overall description of the FEM-PrEP adherence counseling support program is provided below, including counselor and pharmacist main messages for participants. Details on the adherence counseling program can be found elsewhere.

### A. Adherence counseling support program summary

FEM-PrEP used several different approaches to support participant adherence:

- **Incorporated socio-behavioral preparedness data into the adherence support program.** The FEM-PrEP study teams conducted in-depth interviews with potential participants at several sites before the trial began in order to identify factors that might facilitate or serve as barriers to the use of the study pill. They also talked to women about the best way to incorporate pill-taking into their daily lives. These data were incorporated into counseling procedures and messages to support adherence.

- **Implemented a vitamin "run-in" period.** Participants were given an opportunity to practice taking a pill daily before being given the study pill. Between screening and enrollment, participants were asked to take one vitamin at the same time each day. The vitamins were similar in size to the study pill. Potential facilitators and barriers that might have helped or hindered adherence during the vitamin run-in period were discussed during adherence counseling at enrollment. Counselors then helped the participants to develop targeted plans for adherence to the study regimen based on her experience with the daily vitamin taking. In addition, as part of the trial's eligibility criteria, each woman was asked to take a vitamin in front of study staff at enrollment; those who could not swallow the tablet could not be enrolled in the study.

- **Provided participant-centered and goal-oriented adherence counseling.** Together with trained counselors, participants developed their own adherence plans by focusing on how to integrate pill-taking into their daily activities and social context. During each follow-up visit, participants and counselors discussed potential strategies to overcome personal barriers to daily pill-taking, and the participant's adherence plans were refined as needed. Messages about adherence to the study pill were strategically delivered during counseling over the course of the trial. The use of reminders to take pills, such as cell phone alarms, a pill box, and a calendar, was encouraged. Pharmacists also provided brief messages on adherence when distributing the study pill.

- **Enhanced adherence counseling based on real-time data.** Self-reported adherence data were collected monthly during the implementation of the trial; these data were reviewed regularly to improve adherence support provided to participants. For example, these data were used to identify the reasons that participants did not take the study pill or to examine whether pill fatigue was occurring over time. Counselors then used this information to devise strategies to enhance support for adherence. At some sites, a random sample of participants was interviewed periodically about their experiences with adherence. Data from these in-depth interviews were analyzed and summarized for study staff so the information could be used to enhance support for adherence.

**B. Counselors' messages for participants**

**Nurse/Counselors main adherence messages:**

- Describe pill regimen:
  - Take ONE study pill per day
  - Around the same time each day
  - With or without liquid
  - With or without food
- Ask participants to do their best to take their study pill every day. Otherwise researchers will NOT be able to determine if Truvada is safe and effective for HIV prevention for future generations to use
- Stress the following:
  - Rules for missed study pills
  - Pills are not to be shared or sold
  - Pills need to be taken whole to find out if they work (Do not split, chew, crush, or dissolve pills)
  - Keep pills out of reach of children
  - Desiccant should not be swallowed or removed from the bottle
- Also explain that:
  - She will not feel an improvement in her health status after taking the study pills
  - The pills may have a bitter taste (the coating helps to reduce bitter taste)
  - She should bring any remaining pills to her next appointment in the pill bottle or pill box
  - She should contact study staff at any time if she has any problems with the study pills
- Congratulate participants for good adherence or encourage improved adherence

**Rules for missed study pills:**

- If you miss a pill, take the pill as soon as you remember on that day before midnight.
- If you do not remember until after midnight that day, do not take the missed pill. Take the pill at the scheduled time the next day. You can only take one pill each day.
- If you forget your pill on any day, leave the extra pill(s) in your pill bottle or pill box; do not throw away the pill.
- Bring any remaining pills with you to your next appointment in the pill bottle or pill box.

- Never take more than 1 pill at a time or in a day.
- Contact the study staff immediately if you lose your bottle of pills or have any questions.

**Reasons for not sharing/selling study pills:**

- Researchers will NOT be able to determine if Truvada is safe and effective for HIV prevention if participants share or sell pills or if they do not take their pills as instructed
- Pills are for you alone
- Pills should not be shared with other participants -- each participant has pills that are hers
- Pills should not be shared with anyone whether they are HIV positive or HIV negative → they will not help an HIV-positive friend or family member
    - These pills are not regular antibiotics:
        - They will have no effect on a chest cold, fever, or urinary tract infection
    - You will NOT know if you are taking Truvada or the placebo because the two pills look exactly alike
    - If you are taking the placebo and it is shared, it will have no health benefit
    - If you are taking Truvada and it is shared:
        - It is unknown if Truvada is safe and effective for HIV prevention
        - Taking just Truvada can lead to resistance among people who are HIV positive, and many people who are HIV positive do not know they are positive
        - People on Truvada need to be followed by a doctor
- If you run out of pills:
    - You cannot borrow pills from another participant -- she may have a different study pill from you
    - Come to the study site to collect more pills from the study pharmacist

**How to open the pill bottle:**

*To remove the cap from the bottle:*

- Press down on the cap and turn the cap to the left
- Keep pressing down and turning the cap to the left until cap is removed

*To replace the cap back on the bottle:*

- Place cap on top of the bottle
- Turn cap to the right until the cap can no longer turn
- Turn cap back to the left to lock (the cap will make a small noise to indicate that it is locked)

*Other information for participants:*

- Keep container tightly closed
- Do not use if seal over bottle opening is broken or missing

**How to use a pill box**

- The use of the pill box is voluntary
- Pill boxes hold 7 days of pills

- The boxes should be filled one week at a time with one pill in each section (7 pills total)
- Each day, the participant will open a new section according to the day of the week on the window and take the pill inside
- The pill box automatically locks each time a section is shut. To open a section, the participant should press down the lock on the left of the pill box then open a section (demonstrate)
- When the week is finished, the participant should refill the pill box with the pills remaining in the pill bottle putting one pill in each section
- Pills not put in the pill box should be kept in the pill bottle along with the desiccant
- If a participant missed a pill, she should leave it in the pill box; she can take it the following week
- Participant should bring the pill bottle and pill box to each study visit

## 15.0 Laboratory procedures

The HIV/STI Reference Laboratory at the Institute of Tropical Medicine (ITM) served as the central laboratory for the trial.

All sites had an on-site laboratory where HIV rapid testing, Hepatitis B surface antigen rapid testing, urine testing and microscopy were performed. The study sites worked with additional extramural laboratories for CD4 absolute count, *Chlamydia trachomatis*/*Neisseria gonorrhoeae* (CT/NG) amplification testing, syphilis serology, Hepatitis B antibody testing and biochemistry assays where necessary. Laboratory testing was conducted in two laboratories for the study site in Bondo, Kenya (Laboratory of the Bondo Site and University of Nairobi – Institute of Tropical and Infectious Diseases, Kenya), in three laboratories for the Bloemfontein, South Africa site (JOSHA Research Laboratory, PathCare Laboratory South Africa), for the Pretoria, South Africa site (Setshaba Research Center Laboratory, University of Pretoria – NHLS and Global Clinical and Viral Laboratory Durban, South Africa) and for the Arusha, Tanzania site (Arusha Levolosi Research Clinic Laboratory, Kilimanjaro Reproductive Health Program Laboratory and Duke Kilimanjaro Christian Medical Center Biotechnology Laboratory - Tanzania).

### A. Assay selection

Before initiation of the study, the central laboratory gave advice on the selection of the local laboratories, testing algorithms and on the choice of assays to be used for selected study tests. All laboratories were encouraged to create or adapt their own SOPs (Standard Operating Procedures) for all assays whenever possible. The sites could choose their method of analyses for biochemistry, Hepatitis B antibody, CT/NG amplification- and syphilis testing. However, more stringent guidelines were given for HIV and Hepatitis B antigen rapid testing, urine pregnancy and dipstick testing, microscopy and CD4 absolute count analysis. See Table 1 for more detailed information with regard to the different equipment and assays that were used for each of the tests at the respective study sites.

**B. Specimen collection**

- **Serum**: Five 10mL tubes of venous blood were drawn in a plastic uncoated serum tube at the screening visit and at the week 4, 12, 24, 36, 52 and 56 visits. Three 7mL tubes of venous blood were drawn in a plastic uncoated serum tube at the seroconversion visit and at weeks 4, 12, 24, 36, 52 after a positive HIV serology result until no toxicity was detected.

  After centrifugation the serum was collected and used for biochemistry testing. Two aliquots of approximately 1mL of serum each were stored at -20°C for shipment to the central laboratory or for storage for future research.

- **Plasma:** 10mL of venous blood was drawn in a plastic EDTA tube at enrollment and at all regular follow up visits. If a participant tested positive for HIV antibodies according to the study algorithm, a second sample of 10mL of venous blood was drawn in a plastic EDTA tube.

  Two 10mL tubes of venous blood were drawn in a plastic EDTA tube at seroconversion visit and at weeks 4, 12, 24, 36, and 52 and one tube of 10mL of venous blood was drawn in a plastic EDTA tube at week 8 and 16 from the seroconverters post HIV diagnosis.

  Within four hours of sample collection, the 10mL EDTA tube was centrifuged at 800 x g (± 2000-2200 rpm) at room temperature for ten minutes. The plasma was transferred, whenever possible under sterile conditions, into a sterile 15mL conical tube. The tube was centrifuged for 30 minutes at 1200 x g (± 2200 - 2400 rpm) at room temperature. A minimum of four vials (example 1.5 mL Nalgene model '5000 cryogenic vial system 100') containing a minimum of 1mL of plasma were prepared per ten mL EDTA tube and stored at -70°C in a vertical position.

  HIV antibody testing was performed on the plasma obtained after the first centrifugation.

  Aliquots were tested by the study sites for HIV viral load if requested for patient clinical management, for resistance testing by Gladstone Institute of Virology and Immunology, for HIV PCR, HIV viral load and HIV serology quality control by the central laboratory and for Tenofovir and Emtricitabine drug level measurement by the University of North Carolina. The other aliquots were stored on site at -70°C for possible future research.

- **Upper Layer Packed Cells (ULPC):** Approximately 1mL of ULPC left over from the plasma sample was transferred into a cryotube and stored at -20°C in a vertical position until shipment to the central laboratory for HIV DNA PCR and/or drug level detection.

**C. Testing procedures**

- **HIV testing** was performed on plasma by serial testing using Determine HIV-1/2 (Inverness Medical Innovations Inc., Bedford, UK), Uni-Gold HIV (Trinity Biotech plc, Bray, Ireland), and SD Bioline HIV-1/2 (Standard Diagnostics inc., Suwon city, Kyonggi province, Korea) from enrollment until the first follow up visit after seroconversion. The HIV study algorithm (see

Figure 1) was as follows: specimens were first tested with the Determine HIV-1/2 rapid test, if the Determine HIV-1/2 was not reactive, the final result was considered negative. If Determine HIV-1/2 was reactive, then Uni-Gold HIV was performed. If both the Determine HIV-1/2 and the Uni-Gold HIV tests were reactive, the final result was considered HIV positive. If the Determine HIV-1/2 and Uni-Gold HIV tests were discordant, SD Bioline HIV-1/2 was performed. The final result was considered HIV positive when the SD Bioline was reactive and negative when the SD Bioline was not reactive. The participant was informed about her positive serostatus at enrollment or regular follow-up visits only after retesting and confirmation of the positive result on a second new plasma sample. The second plasma sample was obtained from the participant at the same visit or the next follow-up visit and tested using the HIV study algoithm. During the screening visit, HIV testing was performed on serum or whole blood according to the site-specific national HIV algorithm or the HIV study algorithm.

- **Urine testing:** hCG Pregnancy testing was performed at every visit before seroconversion. After seroconversion pregnancy testing was performed every three months. Urine was also tested by dipstick forprotein and glucose at screening, enrollment and when clinically indicated. If the protein test or glucose test was ≥ 1+, the testing was repeated on a second newly collected urine sample.

- **Hepatitis B testing:** Hepatitis B antigen rapid testing (Determine HBsAg, Inverness Medical Innovations Inc., Bedford, UK) was performed on serum collected at screening, at week 52, at any time of product interruption or withdrawal and when clinically indicated. If the Hepatitis B antigen test result was negative at screening a Hepatitis B antibody test was performed.

- **Syphilis testing:** Syphilis testing was performed at screening and when clinically indicated on serum using the national or local testing algorithm.

- ***Chlamydia trachomatis*/*Neisseria gonorrhoeae* (CT/NG) nucleic acid testing:** Endocervical swabs were collected at screening, at any time of product withdrawal(regular follow up week 52, seroconversion visit or when clinically indicated) and when clinically indicated. The swabs were tested at the extramural laboratories of the study sites.

- **Microscopy:** Two vaginal swabs collected at screening, and at any time of product withdrawal (regular follow up week 52, seroconversion visit or when clinically indicated) and when clinically indicated were used to perform the following microscopy testing:

    - **Wet mount testing*:*** Wet mount microscopy was performed to detect *Trichomonas vaginalis* and yeast cells. The swabs were immediately tested at the respective study site.

    - **Nugent's score*:*** The vaginal smears were Gram stained and scored according to Nugent for the diagnosis of bacterial vaginosis.

- **ALT/AST/phosphorus/creatinine testing:** Determination and quantification of AST/ALT, phosphorus and serum creatinine, and if needed serum $CO_2$, were performed on serum at

screening and at follow up weeks 4, 12, 24, 36, 52 and 56. When a participant seroconverted serum was also taken at at the seroconversion visit and at weeks 4, 12, 24, 36, 52 after a positive HIV serology result until no toxicity was detected

- **CD4 absolute count:** CD4 absolute count was performed using Trucount tubes on BD Facscount or BD Facscalibur. Specimens (3mL of venous blood in a plastic EDTA tube or 2mL of venous blood in BD vacutainer CD4 stabilization tube) collected at the seroconversion visit and at weeks 4, 8, 12, 16, 24, 36 and 52 post post seroconversion visit were tested.

- **HIV NAATs (nucleic acid amplification tests):** included HIV DNA PCR and HIV RNA PCR and were performed by the central laboratory. Viral load testing was performed by some of the on-site laboratories for clinical patient management; however, only viral load results from tests performed by the central laboratory (Cobas AmpliPrep/Cobas TaqMan HIV-1 v2.0, Roche Molecular Systems, Inc., Branchburg, USA) were used for data analysis. Quantitative HIV RNA PCR was performed on samples from the seroconversion visit and weeks 4, 8, 12, 16, 24, 36, 52 post seroconversion. Plasma specimens collected at visit(s) prior to the seroconversion visit were tested in a look-back procedure until the last HIV PCR negative plasma specimen was detected. ULPC of plasma specimens that were negative using the HIV RNA PCR in the look-back procedure were tested using HIV DNA PCR. HIV DNA PCR testing was performed in a look-back procedure until a negative result was obtained. An in-house HIV DNA PCR was performed according to Fransen K et al. Mol (Cell Probes (1994) 8:317-322 and Van Damme et al. Journal of Virological Methods (1995) 51:305-316). In summary, one million peripheral mononuclear cells were analyzed using two independent nested PCR assays for the presence of HIV-1 DNA, targeting the *pol* and the *env* region of HIV-1, respectively. In case of discordant results a third PCR assay was performed amplifying a target within the LTR region. A specimen was considered positive for HIV-1 DNA when two amplification assays with different targets were positive.

- **Drug level analysis (completed at the University of North Carolina at Chapel Hill)**: Tenofovir (TFV) and emtricitabine (FTC) were measured in plasma samples using protein precipitation and LC-MS/MS detection. TFV and FTC were obtained from the NIH AIDS Reference Reagent Program and deuterated internal standards for TFV and FTC were obtained from Moravek Biochemicals, Inc. TFV and FTC were extracted from EDTA-anticoagulated human plasma utilizing acetonitrile protein precipitation containing the internal standards. The analytes were injected using an Agilent ULPC 1200 series stack, separated by a 2.1 x 50 mm, 3µm Water Atlantis™ T3 C-18 analytical column, and detected by an Agilent 6410 LC-MS/MS instrument running Masshunter Workstation Software. The aqueous mobile phase consisted of 0.1% formic acid in 99.9% water and the organic mobile phase consist of 0.1% formic acid in 99.9 % acetonitrile. The retention times for TFV and FTC were 1.3 min. and 3.9 min, respectively. The linear calibration curve ranged from 0.25 ng/mL to 2,500 ng/mL. Intra-assay accuracy ranged from 98-112% and inter-assay accuracy ranged from 95-105%. Intra-assay precision ranged from 4-13% and inter-assay precision ranged from 5-9%.

- **Resistance testing (completed at the Gladstone Institute of Virology and Immunology):** HIV-1 resistance testing was performed using genotypic (TRUGENE, Siemens) and phenotypic (PhenoSense, Monogram Biosciences) tests.

## 16.0 Resistance result details

We did not observe any RT K65R or K70E mutations which cause resistance to TFV.

We detected five mutations that cause resistance to FTC. One HIV seroconverter in the placebo arm and three in the TDF/FTC arm were infected with an RT M184V mutant strain.

- The participant in the placebo arm seroconverted at week 32, her window of infection was week 16-20. The mutation was observed at weeks 20, 24, 28 and 32. The K103N mutation was also detected. This mutation causes resistance to non-nucleoside reverse transcriptase inhibitors and cannot be caused by TDF or FTC. There are no samples from her beyond the seroconversion visit. Drug levels were undetectable and this is likely a transmitted resistance.

- In one participant in the active arm, who seroconverted at week 52, with a window of infection week 44-48 and who had been of product since week 4, with undetectable drug levels at the start and end of her window of HIV infection, the M184V mutation was detected at week 48, week 52 (the seroconversion visit), four and 12 weeks post-seroconversion, but not at later visits. This is thus probably a transmitted resistance.

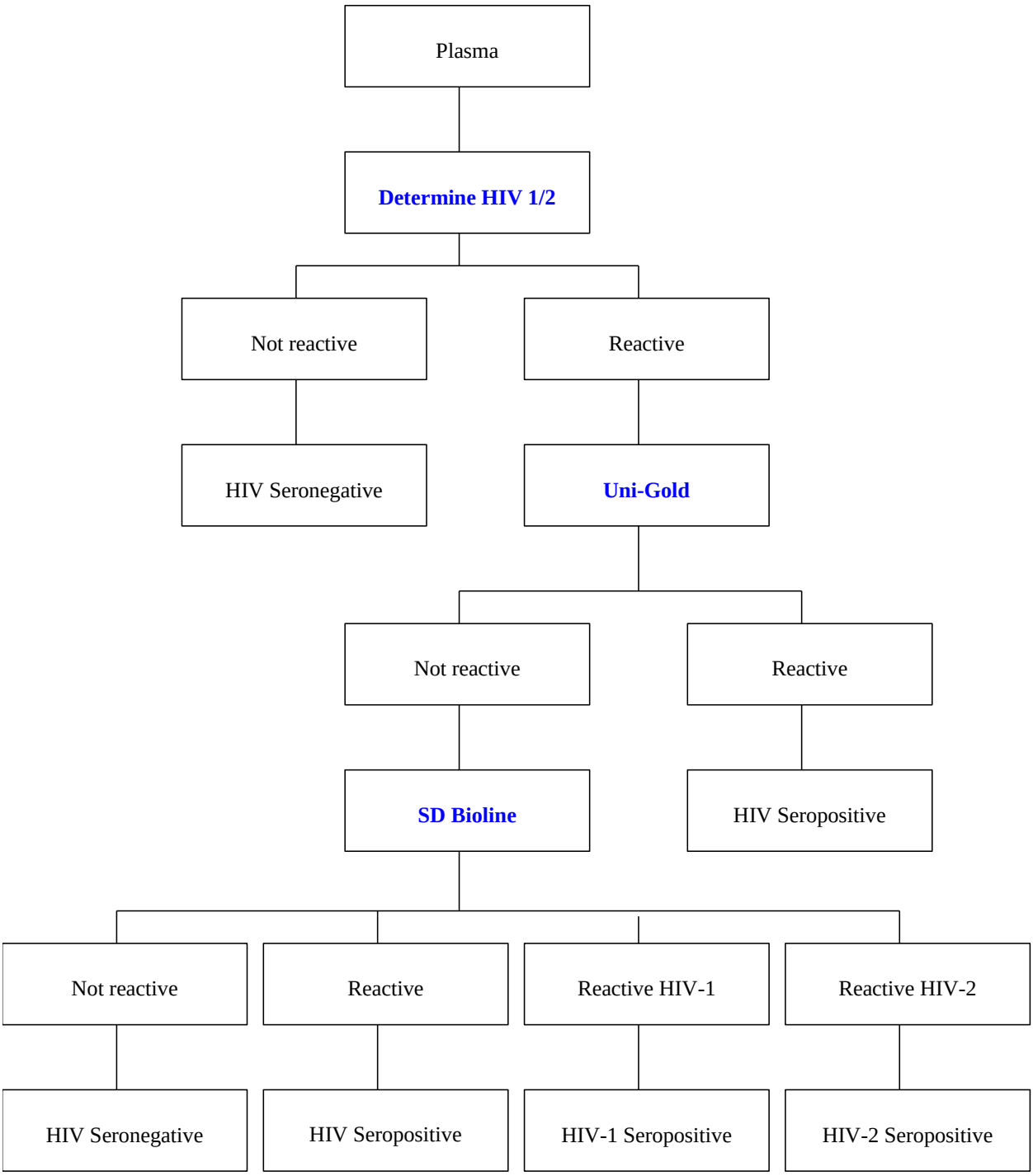
- In a second participant, the mutation was detected at the seroconversion visit and four weeks later; she had no specimens available for subsequent testing until 36 weeks post-seroconversion at which time the mutation was not detected anymore. Her window of infection was enrollment-week 4 and drug was detected in the week 4 sample. A K103N mutation was also observed. Therefore, this may also be a transmitted resistance.

- In the third case, the mutation was observed one, four and eight weeks after the seroconversion visit; twelve weeks post-seroconversion the observed mutation was M184MV. No mutations were observed in later samples. Her window of infection was enrollment-week 8, no drug was detected at week 8, and she missed her week 4 visit due to illness. This could be a transmitted resistance or an incubating infection at enrollment with acquired resistance subsequently.

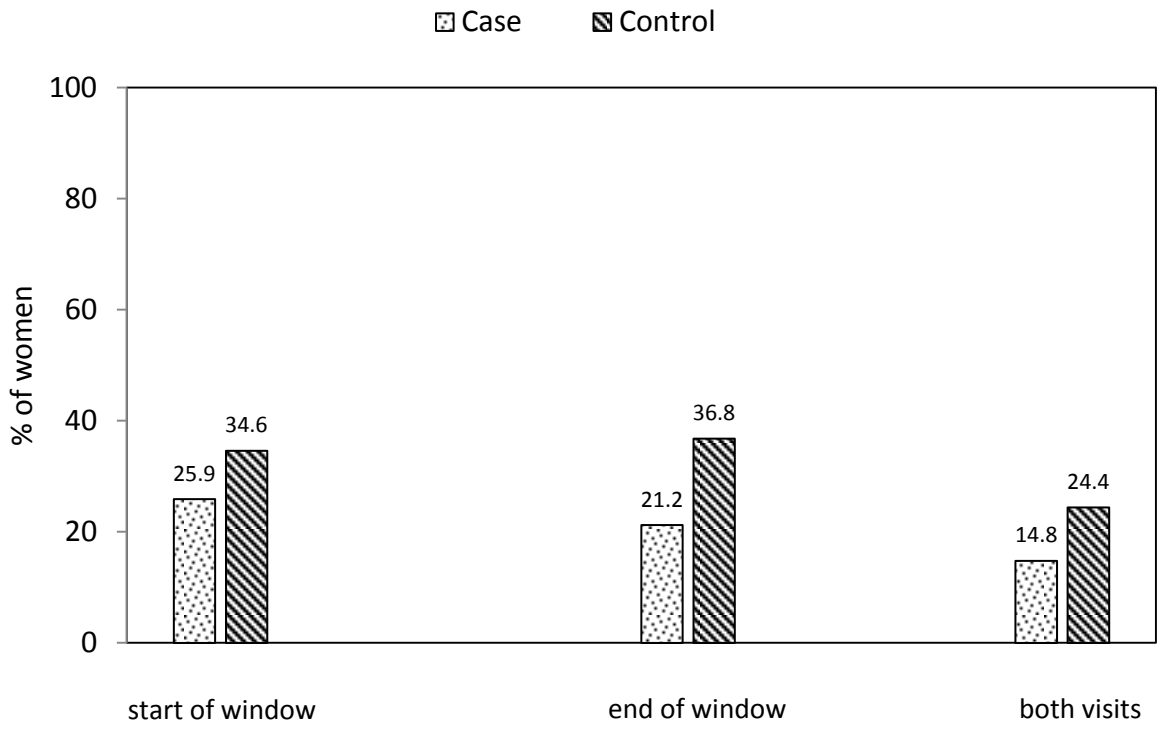
- The fourth seroconverter with a resistant infection in the TDF/FTC arm had a virus strain with an M184I mutation at the seroconversion visit which was not observed four weeks later. Her window of infection was enrollment-week 4 and drug was detected in the week 4 sample. This may also have been an incubating infection at enrollment with acquired resistance subsequently.

Phenotypic testing was successful in the four resistant infections in the TDF/FTC group and failed in the participant assigned to placebo. The results confirmed resistance to FTC and lamivudine; in addition, two of the TDF/FTC arm cases had HIV-1 with increased susceptibility to zidovudine, TDF or both.

## Figure S1: HIV Testing Algorithm



## Figure S2. Plasma Tenofovir Concentration Data for Infected Cases and Uninfected Matched Controls in TDF/FTC Group.




Percent of women with ≥10 ng/ml TFV in plasma at start of infection window (last visit with no evidence of infection), end of window (first visit with evidence of infection), or both visits for 33 infected cases and 95 controls matched on study site and time to event. Only end of window results include specimens from six cases and 17 controls for whom the infection window started before drug was supplied.

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| SOC/Preferred Term | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| **Blood and lymphatic system disorders** | **1 (0.1)** | **1 (0.1)** | **0 (0.0)** | **1 (0.1)** | **0 (0.0)** | **4 (0.3)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **1 (0.1)** | **5 (0.5)** |
| ....Anaemia | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 4 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 5 (0.5) |
| ....Lymphadenopathy | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| **Cardiac disorders** | **2 (0.2)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** |
| ....Palpitations | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Congenital, familial and genetic disorders** | **0 (0.0)** | **1 (0.1)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** |
| ....Exomphalos | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Ear and labyrinth disorders** | **0 (0.0)** | **2 (0.2)** | **0 (0.0)** | **3 (0.3)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **2 (0.2)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** |
| ....Ear pain | 0 (0.0) | 2 (0.2) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Otorrhoea | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Eye disorders** | **1 (0.1)** | **2 (0.2)** | **0 (0.0)** | **3 (0.3)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **3 (0.2)** | **1 (0.1)** | **2 (0.2)** | **0 (0.0)** | **0 (0.0)** |
| ....Eye pain | 0 (0.0) | 2 (0.2) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Abnormal vision | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Dry eye | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Eye pruritus | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Photophobia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Vision blurred | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Visual acuity reduced | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| **Gastrointestinal disorders** | **76 (6.5)** | **32 (3.1)** | **12 (1.0)** | **68 (5.5)** | **0 (0.0)** | **1 (0.1)** | **111 (9.0)** | **42 (4.0)** | **17 (1.4)** | **65 (5.5)** | **1 (0.1)** | **3 (0.3)** |
| ....Nausea | 24 (2.3) | 4 (0.4) | 5 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 42 (3.9) | 6 (0.6) | 3 (0.3) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| ....Abdominal pain | 12 (1.2) | 5 (0.5) | 1 (0.1) | 9 (0.9) | 0 (0.0) | 0 (0.0) | 12 (1.2) | 10 (1.0) | 2 (0.2) | 3 (0.3) | 0 (0.0) | 0 (0.0) |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| SOC/Preferred Term | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Vomiting | 9 (0.9) | 0 (0.0) | 1 (0.1) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 33 (3.1) | 4 (0.4) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Typhoid fever | 0 (0.0) | 0 (0.0) | 0 (0.0) | 17 (1.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 22 (2.1) | 0 (0.0) | 2 (0.2) |
| ....Gastroenteritis | 0 (0.0) | 2 (0.2) | 0 (0.0) | 13 (1.1) | 0 (0.0) | 1 (0.1) | 3 (0.3) | 3 (0.3) | 2 (0.2) | 12 (1.2) | 0 (0.0) | 1 (0.1) |
| ....Diarrhoea | 16 (1.3) | 4 (0.4) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 12 (1.1) | 3 (0.3) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Dyspepsia | 6 (0.6) | 8 (0.8) | 2 (0.2) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 6 (0.6) | 2 (0.2) | 2 (0.2) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Toothache | 0 (0.0) | 1 (0.1) | 0 (0.0) | 6 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 11 (0.9) | 0 (0.0) | 0 (0.0) |
| ....Gastritis | 1 (0.1) | 1 (0.1) | 1 (0.1) | 8 (0.8) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 2 (0.2) | 1 (0.1) | 4 (0.4) | 0 (0.0) | 0 (0.0) |
| ....Dysentery | 0 (0.0) | 1 (0.1) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (0.7) | 0 (0.0) | 0 (0.0) |
| ....Flatulence | 5 (0.5) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 1 (0.1) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Dental caries | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| ....Peptic ulcer | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Abdominal distension | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Aphthous stomatitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Colitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Constipation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Haemorrhoids | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Cheilitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Gingival pain | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Gingivitis | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Hyperphagia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Mouth ulceration | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Odynophagia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Rectal haemorrhage | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| SOC/Preferred Term | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Rectal prolapse | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Stomatitis | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Umbilical hernia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **General disorders and administration site conditions** | **15 (1.4)** | **9 (0.9)** | **1 (0.1)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **18 (1.8)** | **7 (0.7)** | **3 (0.3)** | **6 (0.5)** | **1 (0.1)** | **0 (0.0)** |
| ....Fatigue | 4 (0.4) | 3 (0.3) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 14 (1.4) | 1 (0.1) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Malaise | 7 (0.7) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 1 (0.1) | 1 (0.1) | 3 (0.3) | 0 (0.0) | 0 (0.0) |
| ....Pain | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Oedema peripheral | 2 (0.2) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Pyrexia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| ....Chills | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Local swelling | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Procedural pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Thirst | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Hepatobiliary disorders** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** |
| ....Cholecystitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| **Immune system disorders** | **17 (1.5)** | **13 (1.3)** | **4 (0.4)** | **10 (1.0)** | **0 (0.0)** | **0 (0.0)** | **25 (2.1)** | **20 (2.0)** | **11 (1.0)** | **6 (0.5)** | **0 (0.0)** | **0 (0.0)** |
| ....Dermatitis allergic | 6 (0.6) | 7 (0.7) | 4 (0.4) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 17 (1.5) | 6 (0.6) | 8 (0.8) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| ....Pruritus allergic | 4 (0.4) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (0.5) | 4 (0.4) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Conjunctivitis allergic | 2 (0.2) | 2 (0.2) | 0 (0.0) | 5 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Hypersensitivity | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 5 (0.5) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Rhinitis allergic | 4 (0.3) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Allergic cough | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Allergic sinusitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| SOC/Preferred Term | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Idiopathic urticaria | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Infections and infestations** | **19 (1.5)** | **270 (19.7)** | **3 (0.2)** | **408 (21.5)** | **0 (0.0)** | **11 (1.0)** | **19 (1.5)** | **259 (18.1)** | **3 (0.3)** | **381 (20.9)** | **0 (0.0)** | **10 (1.0)** |
| ....Malaria | 4 (0.2) | 6 (0.5) | 0 (0.0) | 145 (10.9) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 12 (1.1) | 1 (0.1) | 138 (10.6) | 0 (0.0) | 3 (0.3) |
| ....Respiratory tract infection | 0 (0.0) | 33 (3.1) | 0 (0.0) | 91 (7.4) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 29 (2.8) | 2 (0.2) | 76 (6.6) | 0 (0.0) | 0 (0.0) |
| ....Vaginitis bacterial | 5 (0.5) | 61 (5.9) | 0 (0.0) | 12 (1.2) | 0 (0.0) | 0 (0.0) | 4 (0.4) | 53 (5.1) | 0 (0.0) | 9 (0.9) | 0 (0.0) | 0 (0.0) |
| ....Candidiasis | 5 (0.5) | 45 (4.0) | 0 (0.0) | 7 (0.7) | 0 (0.0) | 0 (0.0) | 6 (0.6) | 40 (3.8) | 0 (0.0) | 16 (1.5) | 0 (0.0) | 0 (0.0) |
| ....Chlamydial infection | 1 (0.1) | 33 (3.2) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 32 (3.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Urinary tract infection | 0 (0.0) | 13 (1.3) | 0 (0.0) | 25 (2.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 18 (1.8) | 0 (0.0) | 1 (0.1) |
| ....Nasopharyngitis | 0 (0.0) | 19 (1.7) | 0 (0.0) | 23 (1.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 12 (1.1) | 0 (0.0) | 9 (0.9) | 0 (0.0) | 0 (0.0) |
| ....Tonsillitis | 1 (0.1) | 4 (0.4) | 0 (0.0) | 20 (1.7) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 9 (0.8) | 0 (0.0) | 17 (1.5) | 0 (0.0) | 1 (0.1) |
| ....Tinea infection | 0 (0.0) | 8 (0.8) | 1 (0.1) | 13 (1.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (0.8) | 0 (0.0) | 10 (1.0) | 0 (0.0) | 0 (0.0) |
| ....Pelvic inflammatory disease | 1 (0.1) | 9 (0.9) | 0 (0.0) | 9 (0.9) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 10 (1.0) | 0 (0.0) | 6 (0.6) | 0 (0.0) | 0 (0.0) |
| ....Vaginal infection | 0 (0.0) | 2 (0.2) | 0 (0.0) | 10 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (0.5) | 0 (0.0) | 19 (1.6) | 0 (0.0) | 0 (0.0) |
| ....Trichomoniasis | 1 (0.1) | 6 (0.6) | 0 (0.0) | 8 (0.8) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 9 (0.9) | 0 (0.0) | 0 (0.0) |
| ....Influenza | 1 (0.1) | 11 (1.0) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 10 (1.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) |
| ....Pneumonia | 0 (0.0) | 0 (0.0) | 2 (0.1) | 11 (1.1) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 2 (0.2) | 0 (0.0) | 9 (0.8) | 0 (0.0) | 1 (0.1) |
| ....Cervicitis | 0 (0.0) | 3 (0.3) | 0 (0.0) | 7 (0.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 10 (1.0) | 0 (0.0) | 0 (0.0) |
| ....Abscess | 0 (0.0) | 4 (0.4) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 5 (0.5) | 0 (0.0) | 1 (0.1) |
| ....Gonorrhoea | 0 (0.0) | 5 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 7 (0.7) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| ....Sinusitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 5 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Furuncle | 0 (0.0) | 1 (0.1) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) |
| ....Tuberculosis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 2 (0.2) |
| ....Vulvovaginitis | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| SOC/Preferred Term | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Wound infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) |
| ....Eye infection | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| ....Oral herpes | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 3 (0.3) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Pharyngitis | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Herpes zoster | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Otitis externa | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Pyelonephritis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Helminthic infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Hordeolum | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Otitis media | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Amoebiasis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Bartholin's abscess | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| ....Bronchopneumonia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Cellulitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Ear infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Extrapulmonary tuberculosis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Herpes simplex | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Parotitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Rhinitis | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Injury, poisoning and procedural complications** | **1 (0.1)** | **9 (0.9)** | **0 (0.0)** | **10 (0.9)** | **1 (0.1)** | **3 (0.3)** | **0 (0.0)** | **9 (0.9)** | **0 (0.0)** | **8 (0.8)** | **1 (0.1)** | **3 (0.3)** |
| ....Wound | 0 (0.0) | 4 (0.4) | 0 (0.0) | 6 (0.6) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| ....Joint sprain | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| ....Animal bite | 0 (0.0) | 2 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| SOC/Preferred Term | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Fracture[1] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| ....Human bite | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Incision site pain | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Periorbital haematoma | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Thermal burn | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| ....Abdominal injury | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| ....Anthropod sting | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Contusion | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Contusion of knee | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Face injury | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Injury | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Mouth injury | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Tooth fracture | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Investigations** | **307 (22.4)** | **219 (14.8)** | **164 (12.9)** | **3 (0.3)** | **34 (3.1)** | **0 (0.0)** | **396 (26.8)** | **204 (15.0)** | **174 (14.0)** | **4 (0.4)** | **35 (2.7)** | **1 (0.1)** |
| ....Blood phosphorus decreased | 74 (6.1) | 3 (0.3) | 148 (11.8) | 2 (0.2) | 30 (2.7) | 0 (0.0) | 96 (7.6) | 2 (0.2) | 139 (11.9) | 3 (0.3) | 27 (2.1) | 0 (0.0) |
| ....Aspartate aminotransferase increased | 42 (3.8) | 99 (8.6) | 5 (0.5) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 60 (5.4) | 99 (8.5) | 12 (1.2) | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| ....Alanine aminotransferase increased | 84 (7.3) | 12 (1.2) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 125 (9.6) | 7 (0.7) | 7 (0.7) | 0 (0.0) | 2 (0.1) | 0 (0.0) |
| ....Blood phosphorus increased | 14 (1.4) | 98 (7.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (0.5) | 90 (7.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Blood creatinine increased | 61 (5.1) | 3 (0.2) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 74 (5.5) | 2 (0.2) | 6 (0.5) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| ....Liver function test abnormal | 13 (1.3) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 23 (2.0) | 1 (0.1) | 6 (0.6) | 0 (0.0) | 4 (0.4) | 0 (0.0) |
| ....Blood bicarbonate decreased | 19 (1.7) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 10 (1.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| SOC/Preferred Term | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Eosinophil count increased | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Platelet count increased | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Creatinine renal clearance decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Glucose urine | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Haemoglobin decreased | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Heart rate decreased | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Hormonal level abnormal | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Renal function test abnormal | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Weight decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Metabolism and nutrition disorders** | **3 (0.3)** | **3 (0.3)** | **1 (0.1)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **7 (0.7)** | **1 (0.1)** | **3 (0.3)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** |
| ....Decreased appetite | 0 (0.0) | 3 (0.3) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (0.6) | 1 (0.1) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Anorexia | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Dehydration | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Musculoskeletal and connective tissue disorders** | **6 (0.6)** | **29 (2.7)** | **0 (0.0)** | **30 (2.6)** | **0 (0.0)** | **2 (0.2)** | **2 (0.2)** | **32 (3.1)** | **0 (0.0)** | **29 (2.7)** | **0 (0.0)** | **0 (0.0)** |
| ....Back pain | 3 (0.3) | 16 (1.5) | 0 (0.0) | 7 (0.7) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 9 (0.9) | 0 (0.0) | 11 (1.1) | 0 (0.0) | 0 (0.0) |
| ....Arthralgia | 0 (0.0) | 4 (0.4) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (0.8) | 0 (0.0) | 7 (0.7) | 0 (0.0) | 0 (0.0) |
| ....Myalgia | 1 (0.1) | 5 (0.5) | 0 (0.0) | 6 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| ....Soft tissue injury | 1 (0.1) | 0 (0.0) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (0.6) | 0 (0.0) | 3 (0.2) | 0 (0.0) | 0 (0.0) |
| ....Musculoskeletal chest pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Arthritis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| ....Neck pain | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Musculoskeletal stiffness | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Joint contracture | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| SOC/Preferred Term | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Joint dislocation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Muscle mass | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Osteitis | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Pain in extremity | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Synovial cyst | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Nervous system disorders** | **121 (9.7)** | **59 (5.1)** | **25 (2.1)** | **23 (2.2)** | **1 (0.1)** | **0 (0.0)** | **122 (10.0)** | **56 (5.1)** | **32 (2.8)** | **14 (1.4)** | **6 (0.5)** | **0 (0.0)** |
| ....Headache | 81 (7.1) | 49 (4.4) | 21 (1.8) | 22 (2.1) | 0 (0.0) | 0 (0.0) | 65 (6.1) | 43 (4.0) | 30 (2.7) | 13 (1.3) | 2 (0.2) | 0 (0.0) |
| ....Dizziness | 36 (3.4) | 7 (0.7) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 45 (4.1) | 10 (1.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Hypoaesthesia | 1 (0.1) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (0.4) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Neuropathy peripheral | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) |
| ....Syncope | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) |
| ....Paraesthesia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Insomnia | 1 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Somnolence | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Burning sensation | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Hemiparesis | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Muscular weakness | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| ....Neuritis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Vision blurred | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Pregnancy, puerperium and perinatal conditions** | **0 (0.0)** | **1 (0.1)** | **3 (0.3)** | **3 (0.3)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **4 (0.4)** | **0 (0.0)** | **4 (0.4)** | **1 (0.1)** | **11 (1.1)** |
| ....Abortion | 0 (0.0) | 1 (0.1) | 3 (0.3) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 4 (0.4) | 1 (0.1) | 5 (0.5) |
| ....Ectopic pregnancy | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) |
| ....Foetal distress syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| SOC/Preferred Term | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Vomiting in pregnancy | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Abortion threatened | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| ....Premature rupture of the membranes | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| ....Somatoform disorder pregnancy | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Psychiatric disorders** | **1 (0.1)** | **1 (0.1)** | **0 (0.0)** | **2 (0.2)** | **0 (0.0)** | **3 (0.3)** | **0 (0.0)** | **1 (0.1)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** |
| ....Intentional overdose | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| ....Anxiety | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Depression | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Mood swings | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Panic attack | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Withdrawal syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Renal and urinary disorders** | **0 (0.0)** | **1 (0.1)** | **1 (0.1)** | **2 (0.2)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **3 (0.3)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** |
| ....Dysuria | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Proteinuria | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Haematuria | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Urinary incontinence | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Reproductive system and breast disorders** | **10 (0.9)** | **38 (3.4)** | **0 (0.0)** | **31 (2.9)** | **0 (0.0)** | **1 (0.1)** | **4 (0.4)** | **44 (3.8)** | **0 (0.0)** | **38 (3.5)** | **0 (0.0)** | **1 (0.1)** |
| ....Vaginal discharge | 6 (0.5) | 4 (0.4) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 19 (1.6) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| ....Dysfunctional uterine bleeding | 0 (0.0) | 4 (0.4) | 0 (0.0) | 9 (0.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 14 (1.4) | 0 (0.0) | 1 (0.1) |
| ....Metrorrhagia | 1 (0.1) | 11 (1.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 5 (0.5) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) |
| ....Menorrhagia | 0 (0.0) | 3 (0.3) | 0 (0.0) | 5 (0.5) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 8 (0.8) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) |
| ....Dysmenorrhoea | 1 (0.1) | 2 (0.2) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 3 (0.3) | 0 (0.0) | 4 (0.4) | 0 (0.0) | 0 (0.0) |
| ....Genital ulceration | 0 (0.0) | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 8 (0.8) | 0 (0.0) | 0 (0.0) |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| SOC/Preferred Term | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Pelvic pain | 1 (0.1) | 2 (0.2) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Vulvovaginal pruritus | 0 (0.0) | 4 (0.4) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Amenorrhoea | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Premenstrual syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Breast discomfort | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Breast pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Coital bleeding | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Dyspareunia | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Galacthorrhoea | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Genital erosion | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Menometrorrhagia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Ovarian cyst | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Uterine leiomyoma | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Vaginal ulceration | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **2 (0.2)** | **18 (1.5)** | **0 (0.0)** | **10 (0.9)** | **0 (0.0)** | **2 (0.2)** | **1 (0.1)** | **15 (1.5)** | **0 (0.0)** | **10 (1.0)** | **0 (0.0)** | **1 (0.1)** |
| ....Oropharyngeal pain | 0 (0.0) | 2 (0.2) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 6 (0.6) | 0 (0.0) | 6 (0.6) | 0 (0.0) | 0 (0.0) |
| ....Cough | 1 (0.1) | 3 (0.3) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (0.5) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Asthma | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (0.3) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 1 (0.1) |
| ....Epistaxis | 1 (0.1) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Chest pain | 0 (0.0) | 3 (0.3) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Bronchitis | 0 (0.0) | 3 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Nasal congestion | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Hyperventilation | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| SOC/Preferred Term | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Pleurisy | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Postnasal drip | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Pulmonary congestion | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| **Skin and subcutaneous tissue disorders** | **10 (0.9)** | **8 (0.8)** | **2 (0.2)** | **7 (0.7)** | **0 (0.0)** | **0 (0.0)** | **5 (0.5)** | **9 (0.8)** | **3 (0.3)** | **2 (0.2)** | **0 (0.0)** | **0 (0.0)** |
| ....Rash | 3 (0.3) | 2 (0.2) | 1 (0.1) | 4 (0.4) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Pruritus generalised | 3 (0.3) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Pruritus | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Dermatitis atopic | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Eczema | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Acne | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Angioedema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Chloasma | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Dermatitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Dry skin | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Scar pain | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Skin exfoliation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Skin hyperpigmentation | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Skin hypopigmentation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Skin ulcer | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Urticaria | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Social circumstances** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **0 (0.0)** | **0 (0.0)** |
| ....Physical assault | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| **Surgical and medical procedures** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** |

**Table S1: Adverse Events and Percent of Women with Events, by Severity and Relatedness - Safety Population**

| | Placebo (N=1033) | | | | | | TDF/FTC (N=1025) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild | | Moderate | | Severe/Life Threat | | Mild | | Moderate | | Severe/Life Threat | |
| SOC/Preferred Term | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % | Related n % | Not Related n % |
| ....Removal of foreign body | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Vascular disorders** | **0 (0.0)** | **2 (0.2)** | **0 (0.0)** | **2 (0.2)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **5 (0.5)** | **2 (0.2)** | **1 (0.1)** | **0 (0.0)** | **0 (0.0)** |
| ....Hypertension | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Venous insufficiency | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Hypotension | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| ....Varicose vein | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Lymphoedema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ....Orthostatic hypotension | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Total** | **592 (36.1)** | **718 (42.0)** | **216 (16.5)** | **616 (27.1)** | **36 (3.3)** | **28 (2.5)** | **714 (40.4)** | **717 (43.0)** | **249 (18.3)** | **572 (27.2)** | **46 (3.3)** | **37 (3.3)** |

Related includes all events classified as probably unrelated, possibly related, probably related and definitely related.

[1]This was considered severe/serious because the participant broke her arm and needed to be hospitalized, and potentially product related because the fracture was deemed a serious consequence for a minor fall.

## Table S2: Serious Adverse Events

## Table S2: Serious Adverse Events

| System Organ Class/Preferred Term | Placebo (N =1033) | | | TDF/FTC (N =1025) | | |
|---|---|---|---|---|---|---|
| | # of Events | # of Women | % of Women | # of Events | # of Women | % of Women |
| **Blood and lymphatic system disorders** | **0** | **0** | **( 0.0)** | **2** | **2** | **( 0.2)** |
| Anaemia | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| **Congenital, familial and genetic disorders** | **1** | **1** | **( 0.1)** | **1** | **1** | **( 0.1)** |
| Exomphalos | 1 | 1 | ( 0.1) | 1 | 1 | ( 0.1) |
| **Gastrointestinal disorders** | **2** | **2** | **( 0.2)** | **3** | **3** | **( 0.3)** |
| Typhoid fever | 1 | 1 | ( 0.1) | 2 | 2 | ( 0.2) |
| Gastroenteritis | 1 | 1 | ( 0.1) | 1 | 1 | ( 0.1) |
| **Infections and infestations** | **6** | **5** | **( 0.5)** | **11** | **11** | **( 1.1)** |
| Malaria | 3 | 3 | ( 0.3) | 4 | 4 | ( 0.4) |
| Pneumonia | 1 | 1 | ( 0.1) | 1 | 1 | ( 0.1) |
| Respiratory tract infection | 1 | 1 | ( 0.1) | 1 | 1 | ( 0.1) |
| Tuberculosis | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| Bartholin's abscess | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Influenza | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Pelvic inflammatory disease | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Urinary tract infection | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Injury, poisoning and procedural complications** | **4** | **4** | **( 0.4)** | **4** | **4** | **( 0.4)** |
| Fracture | 2 | 2 | ( 0.2) | 1 | 1 | ( 0.1) |
| Wound | 2 | 2 | ( 0.2) | 1 | 1 | ( 0.1) |
| Abdominal injury | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Joint sprain | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Musculoskeletal and connective tissue disorders** | **2** | **2** | **( 0.2)** | **0** | **0** | **( 0.0)** |
| Joint contracture | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Joint dislocation | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| **Nervous system disorders** | **1** | **1** | **( 0.1)** | **4** | **3** | **( 0.3)** |
| Syncope | 1 | 1 | ( 0.1) | 2 | 2 | ( 0.2) |
| Muscular weakness | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Neuropathy peripheral | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Pregnancy, puerperium and perinatal conditions** | **0** | **0** | **( 0.0)** | **8** | **8** | **( 0.8)** |
| Abortion | 0 | 0 | ( 0.0) | 3 | 3 | ( 0.3) |
| Ectopic pregnancy | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| Foetal distress syndrome | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| Premature rupture of the membranes | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Psychiatric disorders** | **4** | **4** | **( 0.4)** | **1** | **1** | **( 0.1)** |
| Intentional overdose | 2 | 2 | ( 0.2) | 1 | 1 | ( 0.1) |

**Table S2: Serious Adverse Events**

| **System Organ Class/**Preferred Term | **Placebo (N =1033)** | | | **TDF/FTC (N =1025)** | | |
|---|---|---|---|---|---|---|
| | **# of Events** | **# of Women** | **% of Women** | **# of Events** | **# of Women** | **% of Women** |
| Depression | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Withdrawal syndrome | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| **Reproductive system and breast disorders** | **1** | **1** | **( 0.1)** | **0** | **0** | **( 0.0)** |
| Menorrhagia | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **2** | **2** | **( 0.2)** | **1** | **1** | **( 0.1)** |
| Asthma | 2 | 2 | ( 0.2) | 1 | 1 | ( 0.1) |
| **Surgical and medical procedures** | **1** | **1** | **( 0.1)** | **0** | **0** | **( 0.0)** |
| Removal of foreign body | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| **Vascular disorders** | **0** | **0** | **( 0.0)** | **1** | **1** | **( 0.1)** |
| Hypotension | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Total** | **24** | **23** | **( 2.2)** | **36** | **33** | **( 3.2)** |

Number of serious adverse events and the proportion of women experiencing the AE. There were no significant differences in the proportion of women experiencing any given AE type.

## Table S3: Severe or Potentially Life Threatening Events

## Table S3: Severe or Potentially Life Threatening Events

| System Organ Class/Preferred Term | Placebo (N =1033) | | | TDF/FTC (N =1025) | | |
|---|---|---|---|---|---|---|
| | # of Events | # of Women | % of Women | # of Events | # of Women | % of Women |
| **Blood and lymphatic system disorders** | **4** | **3** | **( 0.3)** | **6** | **6** | **( 0.6)** |
| Anaemia | 4 | 3 | ( 0.3) | 6 | 6 | ( 0.6) |
| **Gastrointestinal disorders** | **1** | **1** | **( 0.1)** | **4** | **4** | **( 0.4)** |
| Gastroenteritis | 1 | 1 | ( 0.1) | 1 | 1 | ( 0.1) |
| Typhoid fever | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| Nausea | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **General disorders and administration site conditions** | **0** | **0** | **( 0.0)** | **1** | **1** | **( 0.1)** |
| Pyrexia | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Hepatobiliary disorders** | **0** | **0** | **( 0.0)** | **1** | **1** | **( 0.1)** |
| Cholecystitis | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Infections and infestations** | **11** | **10** | **( 1.0)** | **10** | **10** | **( 1.0)** |
| Malaria | 2 | 2 | ( 0.2) | 3 | 3 | ( 0.3) |
| Tuberculosis | 1 | 1 | ( 0.1) | 2 | 2 | ( 0.2) |
| Pneumonia | 1 | 1 | ( 0.1) | 1 | 1 | ( 0.1) |
| Tonsillitis | 1 | 1 | ( 0.1) | 1 | 1 | ( 0.1) |
| Abscess | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Bartholin's abscess | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Extrapulmonary tuberculosis | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Pelvic inflammatory disease | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Pyelonephritis | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Respiratory tract infection | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Trichomoniasis | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Urinary tract infection | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Wound infection | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| **Injury, poisoning and procedural complications** | **4** | **4** | **( 0.4)** | **4** | **4** | **( 0.4)** |
| Fracture | 2 | 2 | ( 0.2) | 1 | 1 | ( 0.1) |
| Wound | 1 | 1 | ( 0.1) | 1 | 1 | ( 0.1) |
| Abdominal injury | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Joint sprain | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Thermal burn | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Investigations** | **34** | **32** | **( 3.1)** | **36** | **29** | **( 2.8)** |
| Blood phosphorus decreased | 30 | 28 | ( 2.7) | 27 | 22 | ( 2.1) |
| Liver function test abnormal | 4 | 4 | ( 0.4) | 4 | 4 | ( 0.4) |
| Aspartate aminotransferase increased | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| Alanine aminotransferase increased | 0 | 0 | ( 0.0) | 2 | 1 | ( 0.1) |
| Blood creatinine increased | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |

**Table S3: Severe or Potentially Life Threatening Events**

| | Placebo (N =1033) | | | TDF/FTC (N =1025) | | |
|---|---|---|---|---|---|---|
| **System Organ Class/**Preferred Term | **# of Events** | **# of Women** | **% of Women** | **# of Events** | **# of Women** | **% of Women** |
| **Musculoskeletal and connective tissue disorders** | **2** | **2** | **( 0.2)** | **0** | **0** | **( 0.0)** |
| Joint contracture | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Joint dislocation | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| **Nervous system disorders** | **1** | **1** | **( 0.1)** | **6** | **5** | **( 0.5)** |
| Syncope | 1 | 1 | ( 0.1) | 2 | 2 | ( 0.2) |
| Headache | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| Muscular weakness | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Neuropathy peripheral | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Pregnancy, puerperium and perinatal conditions** | **0** | **0** | **( 0.0)** | **12** | **12** | **( 1.2)** |
| Abortion | 0 | 0 | ( 0.0) | 6 | 6 | ( 0.6) |
| Ectopic pregnancy | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| Foetal distress syndrome | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| Abortion threatened | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Premature rupture of the membranes | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Psychiatric disorders** | **3** | **3** | **( 0.3)** | **1** | **1** | **( 0.1)** |
| Intentional overdose | 2 | 2 | ( 0.2) | 1 | 1 | ( 0.1) |
| Depression | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| **Reproductive system and breast disorders** | **1** | **1** | **( 0.1)** | **1** | **1** | **( 0.1)** |
| Dysfunctional uterine bleeding | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Menorrhagia | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **2** | **2** | **( 0.2)** | **1** | **1** | **( 0.1)** |
| Asthma | 2 | 2 | ( 0.2) | 1 | 1 | ( 0.1) |
| **Surgical and medical procedures** | **1** | **1** | **( 0.1)** | **0** | **0** | **( 0.0)** |
| Removal of foreign body | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| **Total** | **64** | **59** | **( 5.7)** | **83** | **65** | **( 6.3)** |

Number of severe or potentially life-threatening AEs and the proportion of women experiencing the AE. Only the difference in proportions of women with abortion-related AEs was significant (Fisher's exact test p=0.02).

## Table S4: Adverse Events leading to Product Use Interruption or Permanent Withdrawal

**Table S4: Adverse Events leading to Product Use Interruption or Permanent Withdrawal**

| | Placebo (N =1033) | | | TDF/FTC (N =1025) | | |
|---|---|---|---|---|---|---|
| **System Organ Class/**Preferred Term | **# of Events** | **# of Women** | **% of Women** | **# of Events** | **# of Women** | **% of Women** |
| **Eye disorders** | **0** | **0** | **( 0.0)** | **1** | **1** | **( 0.1)** |
| Photophobia | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Gastrointestinal disorders** | **0** | **0** | **( 0.0)** | **1** | **1** | **( 0.1)** |
| Nausea | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Infections and infestations** | **1** | **1** | **( 0.1)** | **3** | **3** | **( 0.3)** |
| Tuberculosis | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| Gonorrhoea | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Malaria | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Investigations** | **35** | **31** | **( 3.0)** | **74** | **48** | **( 4.7)** |
| Blood phosphorus decreased | 20 | 20 | ( 1.9) | 32 | 27 | ( 2.6) |
| Blood creatinine increased | 5 | 5 | ( 0.5) | 20 | 16 | ( 1.6) |
| Blood bicarbonate decreased | 2 | 2 | ( 0.2) | 7 | 7 | ( 0.7) |
| Liver function test abnormal | 2 | 2 | ( 0.2) | 8 | 7 | ( 0.7) |
| Alanine aminotransferase increased | 3 | 3 | ( 0.3) | 5 | 4 | ( 0.4) |
| Blood phosphorus increased | 2 | 2 | ( 0.2) | 0 | 0 | ( 0.0) |
| Aspartate aminotransferase increased | 1 | 1 | ( 0.1) | 0 | 0 | ( 0.0) |
| Glucose urine | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Renal function test abnormal | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Nervous system disorders** | **0** | **0** | **( 0.0)** | **4** | **3** | **( 0.3)** |
| Headache | 0 | 0 | ( 0.0) | 2 | 2 | ( 0.2) |
| Muscular weakness | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| Neuropathy peripheral | 0 | 0 | ( 0.0) | 1 | 1 | ( 0.1) |
| **Psychiatric disorders** | **1** | **1** | **( 0.1)** | **1** | **1** | **( 0.1)** |
| Intentional overdose | 1 | 1 | ( 0.1) | 1 | 1 | ( 0.1) |
| **Renal and urinary disorders** | **1** | **1** | **( 0.1)** | **1** | **1** | **( 0.1)** |
| Proteinuria | 1 | 1 | ( 0.1) | 1 | 1 | ( 0.1) |
| **Total** | **38** | **33** | **( 3.2)** | **85** | **55** | **( 5.4)** |

Adverse events leading to interruption or permanent withdrawal of study medication. Difference in proportions of women with blood creatinine increase was significant (Fisher's exact test p=0.02).