Supplementary Appendix

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

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Table S1. Enrollment by Study Site

Country	Site	Date of first enrollment	Total months of site enrollment	Total women screened	Screen/enroll ratio	Total women enrolled
South Africa	**Durban**					
	- Botha's Hill	07-DEC-09	18.0	1,029	2.7	383
	- Chatsworth	25-NOV-09	18.3	1,013	2.4	419
	- eThekwini	20-MAY-10	12.6	772	2.1	360
	- Isipingo	10-MAR-10	14.8	1,124	2.5	451
	- Overport	09-MAR-10	14.9	849	3.5	244
	- Tongaat	09-MAR-10	14.8	1,263	2.9	438
	- Umkomaas	07-APR-10	14.0	919	2.5	365
	- Verulam	09-MAR-10	14.7	1,366	3.0	450
	Johannesburg (WRHI)	14-JUL-10	10.8	731	2.1	354
		13-JUL-10	10.8	589	2.2	263
	Klerksdorp (Aurum)	26-JUL-10	10.4	615	1.8	350
	Soweto (PHRU)					
Uganda	**Kampala**	07-DEC-09	18.0	638	2.0	322
Zimbabwe	**Chitungwiza**					
	- Seke South	02-NOV-09	19.1	420	1.9	217
	- Zengeza	30-NOV-09	18.0	511	2.5	208
	Harare (Spilhaus)	15-SEP-09	20.5	481	2.3	205
Total				12,320	2.4	5,029

Table S2. Study Inclusion and Exclusion Criteria

Inclusion
• Age 18 through 45 years • Able and willing to provide written informed consent and locator information • HIV-uninfected based on testing performed by study staff at screening and enrollment • Sexually active (vaginal intercourse at least once in the past 3 months) • Using effective contraception at enrollment, and intending to use effective method for the next 24 months (including hormonal methods, intrauterine contraceptive device, or sterilization) • Agrees not to join studies of drugs, medical devices, or vaginal products for the next 24 months
Exclusion
• Participant reported any of the following: o Adverse reaction to any of the study products or latex o Pathologic bone fracture not related to trauma (ever) o Non-therapeutic injection drug use in past 12 months o Post-exposure prophylaxis for HIV exposure in past 6 months o Pregnancy outcome or gynecologic or genital procedure in past 42 days o Participation in any other study of drugs, medical devices, or vaginal products in past 30 days o Currently breastfeeding o Currently using spermicide, interferon or interleukin therapy, medication with nephrotoxic potential, or medication inhibiting elimination via active renal tubular secretion o Significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease • Laboratory abnormalities: AST or ALT >1.5 x site ULN, creatinine clearance <60 mL/min, serum creatinine >site ULN, hemoglobin <10.0g/dl, platelet count <100,000/mm, serum phosphate <site LLN, positive HBsAg test, ≥grade 2 Pap result (where standard of care), dipstick urine protein (any result ≥2+ at a single visit, or at least 2 results ≥1+ at separate visits), dipstick urine glucose (any result ≥2+ at single visit, or at least 2 results ≥1+ at separate visits • Pregnancy or intention to become pregnant in next 24 months • Plans to relocate away from site (or travel away for >8 consecutive weeks) in next 24 months • Urinary tract infection • Pelvic inflammatory disease, sexually transmitted infection, or reproductive tract infection • Clinically apparent Grade 2 or higher pelvic exam finding • Any other condition that would preclude informed consent, make participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving study objectives

Note: Detailed criteria are available in the study protocol. ULN = upper limit of normal. LLN = lower limit of normal. In general, women with exclusionary findings could be re-evaluated and enrolled after completing any treatment and findings were resolved. Women with abnormal Pap smears could be enrolled upon completion of initial evaluation if no current treatment was indicated.

Table S3. Study Visits and Procedures

	SCR 1	SCR 2	ENR	MLY	QRT	SEM	ANN	PUEV	TERM
	Up to and including 56 days		Day 0	Must occur -14 days or + 13 days of scheduled visit				Specified in SSP	
Informed Consent	X		X						
Demographics	X								
Locator Information	X	X	X	X	X	X	X	X	X
Behavioral Eligibility	X	X	X						
Review Screen Documentation			X						
Behavioral Risk Assessment			X	X	X	X	X	X	X
Adherence Assessment				X	X	X	X	X	
Prod. Sharing/Dose Recall					X	X	X	X	
Intravaginal Practices Assess.							X	X	X
Social Harms Assessment					X	X	X	X	X
Reimbursement	X	X	X	X	X	X	X	X	X
Schedule Next Visit	▲	▲	▲	X	X	X	X	X	▲
Test Results	X	X	X	X	X	X	X	X	X
Randomization			X						
HIV Pre/Post-Test Couns.	X	▲	X	X	X	X	X	X	X
HIV/STI Risk Red. Couns.	X	X	X	X	X	X	X	X	X
STI/UTI Treatment	▲	▲	▲	▲	▲	▲	▲	▲	▲
Offer HIV Test/Couns. Partners	X	X	X	X	X	X	X	X	X
Offer STI Couns./Tx. Partners	▲	▲	▲	▲	▲	▲	▲	▲	▲
Contraceptive Couns.	X	X	X	X	X	X	X	X	X
Medical Eligibility	X		X						
Med./Mens. History		X	X	X	X	X	X	X	X
Current Medications		X	X	X	X	X	X	X	X
Weight	X	X		■	X	X	X	X	▲
Height		X				X	X	X	
Blood Collection	X	▲	X	X	X	X	X	X	X
Urine Collection	X	X	X	X	X	X	X	X	X
HBsAg	X			▲	▲	▲	▲	X	▲
HBsAb	X			▲	▲	▲	▲	▲	▲
Hepatitis B Vaccination			▲	▲	▲	▲	▲	▲	▲
UA (protein and glucose)	X	▲	+	■	X	X	X	X	▲
UA (nitrites and LE)	X	▲	+	▲	▲	▲	▲	▲	▲
Urine hCG	X	X	X	X	X	X	X	X	X
Urine SDA for GC/CT	X	▲		▲	▲	▲	X	X	▲
Rapid Test-Trichomonas		X	+	▲	▲	▲	X	X	▲
Rapid Test-BV		▲	+	▲	▲	▲	▲	▲	▲
Complete Blood Count	X			▲	▲	X	X	X	▲
Serum Chemistries	X			■	X	X	X	X	▲
Plasma Archive			X	▲	X	X	X	X	X
Blood PK Analyses					X	X	X	X	
Syphilis Serology	X	▲		▲	▲	▲	X	X	▲
HIV Serology	X		X	X	X	X	X	X	X
Physical Exam		X		■	X	X	X	X	▲
Pelvic Exam Visual Inspection		X	+	▲	▲	X	X	X	▲
Vaginal pH		X	+	▲	▲	X	X	X	▲
Vaginal Wet Mount		▲	+	▲	▲	▲	▲	▲	▲
Vag./Endocerv. Swabs Storage		X		▲	▲	X	X	X	▲
Gram Stain		X				X	X	X	
Pap Smear		▲●		▲●	▲●	▲●	▲●	▲●	▲●
Bimanual Exam		X	+	▲	▲	X	X	X	▲
Study Product, Instr., Adher.			X	X	X	X	X		
Condoms	X	X	X	X	X	X	X	X	X
Contraception	▲	▲	▲	▲	▲	▲	▲	▲	▲
Perceived Product Assessment.								X	

X = required, ▲ = as indicated, ● = at sites with capacity where local standard of care, ■ = first monthly visit, + = UA, pelvic exam components, and other relevant assessments may be done on day of ENR to confirm eligibility. *Informed consent for specimen storage and future testing may be deferred (no later than Month 3 follow-up visit). ENR includes procedures conducted as part of final screening procedures and confirmation of eligibility. Monthly visit procedures also occur at quarterly, semiannual, and annual visits;*

likewise, quarterly visit procedures occur at semiannual and annual visits, and semiannual visit procedures occur at annual visits. If Sample 2 is drawn (per Figure 3), blood is also collected for the following analyses: Plasma archive, CD4+ T-cell count, HIV-1 RNA PCR. For hepatitis B susceptible participants randomized to oral study product who do not receive hepatitis B vaccination, HBsAg additionally is checked annually and 6 months after PUEV; serum chemistries are checked 6 months after PUEV.

Table S3A. Schedule of Post-HIV-1 Seroconversion Laboratory Procedures

	Post-Seroconversion Time Points				Time Since Completion of Hepatitis B Vaccine Series
	1-month	3-months	6-months	Q6-months	1 – 2 months
Plasma Archive	X	X	X	X	
HIV-1 RNA PCR	X	X	X	X	
CD4+ T Cell Count	X	X	X	X	
HBsAb					X

Table S3B. Schedule of PBMC Collection

	First QRT	Q 6 Months	INT	PUEV
PBMC Collection at Sites with NL Approval	X*	X	▲	X
TFV-DP and FTC-TP Levels	X*	X	▲	X

*Applies to the participant's first QRT visit following consent for PBMC collection, then every six months thereafter during study participation, plus PUEV.

▲ If a scheduled collection is missed, PBMC should be collected at the next completed visit (scheduled or interim), unless the next visit is less than 4 weeks away from the next scheduled PBMC collection, (in which case collection should occur at the latter visit). Participants who are temporarily held or permanently discontinued from study product should continue to have scheduled PBMC collection unless otherwise specified in the MTN-003 SSP Manual.

Table S4. Institutional Review Boards & Ethics Committees

Clinic Name(s)	Country	City	IRB
Spilhouse, Seke South, Zengeza	Zimbabwe	Harare	Medical Research Council of Zimbabwe (MRCZ) Institutional Review Board
			University of California at San Francisco: Committee on Human Research (CHR)
			MCAZ
Makerere University-JHU Research Collaboration {MUJHU CARE LTD} CRS	Uganda	Kampala	National HIV/AIDs Research Committee (NARC)
			Johns Hopkins University School of Medicine - Johns Hopkins Medicine Institutional Review Board
			Uganda National Council for Science and Technology (UNCST)
Medical Research Council (**MRC**) Sites	South Africa	Durban	Medical Research Council Ethics Committee
			Medicines Control Council
CAPRISA: **eThekwini**	South Africa	Durban	University of Kwazulu-Natal, Nelson R. Mandela School of Medicine: Biomedical Research Ethics Committee
			Medicines Control Council
WRHI	South Africa	Johannesburg	University of the Witwatersrand, Human Research Ethics: (Medical)
			Medicines Control Council
CAPRISA: **Aurum**	South Africa	Klerksdorp	University of Kwazulu-Natal, Nelson R. Mandela School of Medicine: Biomedical Research Ethics Committee
			North West Provincial Research Ethics Committee
			Medicines Control Council
Soweto **PHRU** Clinic	South Africa	Johannesburg	University of the Witwatersrand, Human Research Ethics: (Medical)
			Medicines Control Council

Table S5. Proportion of HIV-1 Seroconverters with Antiretroviral Resistance, by Randomization Arm

Plasma samples for HIV-1 antiretroviral resistance testing were collected as part of Sample 2 a median of 13 days (interquartile range 16 days) after seroconversion was detected and the participant had been withdrawn from study medication (Appendix S4). Resistance testing was successfully completed on plasma from 355/368 (96%) participants, which included 21/22 participants acutely infected at enrollment, 301/312 HIV-1 seroconverters while on study product, and 33/34 participants who seroconverted after their product use end visit (PUEV). 13 participants did not have a resistance result, due to no stored plasma (n = 1), insufficient copies of HIV-1 RNA for extraction (n = 11), and PCR amplification failure (n = 1). Of the 21 participants tested who were acutely infected at enrollment, 16 participants had both their enrollment sample and seroconversion visit sample tested for antiretroviral resistance. 2 participants had only their enrollment sample tested and 3 participants had only their seroconversion visit sample tested due to insufficient RNA copies at other visits.

RNA was extracted from plasma, reverse transcribed, and the HIV-1 *pol* region (codons 1-99 of protease and codons 1-350 of reverse transcriptase) was performed on all seroconverters with plasma HIV-1 RNA levels ≥ 200 copies/ml using the ViroSeq 2.0 Genotyping Method (Celera, Alameda, CA). All sequences were manually edited and nucleotide positions with multiple peaks present at greater than 20% above background were considered mixtures. Resistance mutations were identified using the Stanford Calibrated Population Resistance Tool available on the Stanford HIV-1 Drug Resistance Database (http://hivdb.stanford.edu/) . The laboratory (Microbicides Trials Network Virology Core, University of Pittsburgh School of Medicine Division of Infectious Diseases) was certified to perform ViroSeq Genotyping by the Viral Quality Assurance (VQA) Program of the U.S. National Institutes of Health and by CLIA.

The primary resistance mutations for the study were pre-defined as K65R and K70E (which confer resistance to TDF), and M184I and M184V (which confer resistance to FTC), for their potential to cause a decrease in susceptibility to the study drug. K65R and K70E were not detected in HIV-1 from any participant. Three participants, all who had been randomized to the TDF-FTC arm, were infected with virus that had mutations related to FTC resistance. Two of these participants were retrospectively found to be HIV-1 infected at enrollment with a wild type strain; one developed a mixed viral population of M184M/V after 26 days on study product, and the other developed a mixed viral population of M184M/I/V after 29 days on study product. The third participant had a mixed viral population of M184M/V and was confirmed to be uninfected at enrollment by serology and an undetectable RNA PCR, and seroconversion was detected 309 days after enrollment. Participants who seroconverted after their product use end visit were not infected with resistant strains of HIV-1.

Reverse transcriptase mutation conferring resistance	**TDF**	**FTC/TDF**	**Oral Placebo**	**TFV Gel**	**Gel Placebo**
K65R *confers resistance to TDF*					
Overall	0/70 (0.0%)	0/71 (0.0%)	0/69 (0.0%)	0/71 (0.0%)	0/74 (0.0%)
Among subjects retrospectively found to be HIV-1 infected at enrollment	0/5 (0.0%)	0/9 (0.0%)	0/1 (0.0%)	0/4 (0.0%)	0/2 (0.0%)
Among subjects who acquired HIV-1 after enrollment	0/58 (0.0%)	0/55 (0.0%)	0/60 (0.0%)	0/60 (0.0%)	0/68 (0.0%)
Among subjects who acquired HIV-1 after PUEV	0/7 (0.0%)	0/7 (0.0%)	0/8 (0.0%)	0/7 (0.0%)	0/4 (0.0%)
K70E *confers resistance to TDF*					
Overall	0/70 (0.0%)	0/71 (0.0%)	0/69 (0.0%)	0/71 (0.0%)	0/74 (0.0%)
Among subjects retrospectively found to be HIV-1 infected at enrollment	0/5 (0.0%)	0/9 (0.0%)	0/1 (0.0%)	0/4 (0.0%)	0/2 (0.0%)
Among subjects who acquired HIV-1 after enrollment	0/58 (0.0%)	0/55 (0.0%)	0/60 (0.0%)	0/60 (0.0%)	0/68 (0.0%)
Among subjects who acquired HIV-1 after PUEV	0/7 (0.0%)	0/7 (0.0%)	0/8 (0.0%)	0/7 (0.0%)	0/4 (0.0%)
M184V *confers resistance to FTC*					
Overall	0/70 (0.0%)	3/71 (4.2%)	0/69 (0.0%)	0/71 (0.0%)	0/74 (0.0%)
Among subjects retrospectively found to be HIV-1 infected at enrollment	0/5 (0.0%)	**2/9 (22%)**	0/1 (0.0%)	0/4 (0.0%)	0/2 (0.0%)
Among subjects who acquired HIV-1 after enrollment	0/58 (0.0%)	**1/55 (1.8%)**	0/60 (0.0%)	0/60 (0.0%)	0/68 (0.0%)
Among subjects who acquired HIV-1 after PUEV	0/7 (0.0%)	0/7 (0.0%)	0/8 (0.0%)	0/7 (0.0%)	0/4 (0.0%)
M184I *confers resistance to FTC*					
Overall	0/70 (0.0%)	1/71 (1.4%)	0/69 (0.0%)	0/71 (0.0%)	0/74 (0.0%)
Among subjects retrospectively found to be HIV-1 infected at enrollment	0/5 (0.0%)	**1/9 (11%)**	0/1 (0.0%)	0/4 (0.0%)	0/2 (0.0%)
Among subjects who acquired HIV-1 after enrollment	0/58 (0.0%)	0/55 (0.0%)	0/60 (0.0%)	0/60 (0.0%)	0/68 (0.0%)
Among subjects who acquired HIV-1 after PUEV	0/7 (0.0%)	0/7 (0.0%)	0/8 (0.0%)	0/7 (0.0%)	0/4 (0.0%)

Table S6. Pharmacological measures of adherence and HIV acquisition in VOICE

To assess the prophylactic effect of study products, the detection of tenofovir (TFV) in plasma samples was compared between women who acquired HIV-1 and a random subset of women who did not acquire HIV-1 in the active product arms. The plasma specimens were collected by a case-cohort sampling scheme primarily for quarterly visits, though all available specimens from monthly visits were also included. At the first quarterly visit following enrollment, TFV was detectable in plasma in less than 40% in all three active product groups. Most participants had no plasma drug detected at any quarterly visit during study participation: 58% for the TDF group, 50% for TDF-FTC, and 57% for TFV gel (Figure 1, below). Three ways of assessing the association between TFV detection and HIV acquisition were investigated, detailed below. To control for heterogeneity in HIV-1-related risk behavior among women with plasma TFV detection relative to women without TFV detection, all analyses were adjusted for covariates that predicted both HIV-1 acquisition and plasma TFV detection. These covariates included age greater than 25 years, marital status, having more than 1 child, and independent income. All analyses were also stratified by country. A limitation of these analyses in the interpretation of any associations between TFV detection and HIV-1 acquisition risk is that there is the potential for unmeasured confounders that we were not able to adjust for.

There were approximately 10-15% missing data in quarterly plasma specimens, mostly because participants occasionally missed their visits. A substantial number of seroconverters did not have plasma available from the seroconverting visit (21 of 61 seroconverters in the FTC/TDF oral arm, 19 of 52 seroconverters in the TDF oral arm, 20 of 61 seroconverters in the TFV gel arm). To minimize the impact of missing data, TFV detection at seroconverting visits for some participants were imputed by the last TFV detection status within 90 days. If a participant missed a previous study visit, she would almost always have zero TFV detection (over 95% probability), since participants did not otherwise have access to a new supply of study product. Therefore, all missing TFV detection data that missed the previous visit were imputed to zero.

First, time-varying Cox regression was conducted to examine the association of time-dependent drug detection at monthly or quarterly visits and time to HIV seroconversion. Note that plasma samples were collected primarily quarterly, while HIV testing occurred monthly. In the time-varying Cox regression, the formation of risk set at any seroconverting time requires TFV detection for participants who did not seroconvert at the time. The latter is not always available given the plasma sampling scheme. Therefore the TFV detection status for seronegative participants at any seroconverting point was imputed from the detection status available closest to that visit; unfortunately, this is a major limitation of applying time-varying Cox models to the data on plasma TFV

detection. To account for the case-cohort sampling in the Cox regression analysis with time-varying drug detection status, the *survey* package in R software was used (http://faculty.washington.edu/tlumley/survey/). Use of these imputed data in seroconverters in this analysis did not yield a statistically significant association between drug detection and HIV incidence in any of the three active product arms, possibly due to lack of accuracy in imputation. The results are shown in Table S7A.

Table S6A. Time-Dependent Cox Regression Analysis to Examine the Association of Time-Dependent Drug Detection in Plasma Samples at Monthly or Quarterly Visits and Time to HIV Seroconversion

	No. of seroconversion events deleted due to no plasma data at the seroconverting visit after imputation	Time dependent Cox regression Adjusted Hazard Ratio	95% CI	p-value
TDF/FTC	0	0.49	[0.20,1.21]	0.12
TDF	6	0.53	[0.20,1.37]	0.19
1% TFV gel	5	1.51	[0.71,3.19]	0.29

Second**,** we used a simple measure of adherence, categorizing participants by TFV detection status at the first quarterly visit. This measure was predictive of plasma TFV detection at later quarterly visits, in that those women having no drug detected at their first quarterly visit largely remained having no drug detectable at their subsequent visits. In addition, this measure of adherence was significantly less susceptible to missing data compared to the time-varying Cox analysis. Cox regression analysis was used to assess the association of TFV detection at the first quarterly visit and time to HIV-1 acquisition, and the case-cohort sampling approach was accounted for using the *cch* package in R software. Data from participants for whom their HIV-1 seroconversion event occurred before the first quarterly visit were deleted, as were data from participants who did not have plasma samples from the first quarterly visit after imputation. The results are shown in Table S6B.

Table S6B. Cox Regression Analysis to Assess the Association of TFV Detection in Plasma Samples at the First Quarterly Visit and Time to HIV-1 Acquisition

	No. of sero-converters deleted	No. (%) of women with detectable drug in plasma at their first quarterly visit		First quarterly visit drug detection (Cox regression)	
		Seroconverters	Seronegative	Adjusted HR [95% CI]	p-value
TDF/FTC	4	17/57 (30%)	45/142 (32%)	1.25 [0.61,2.58]	0.54
TDF	9	12/51 (24%)	50/145 (34%)	0.66 [0.31,1.44]	0.30
1% TFV gel	9	6/52 (12%)	50/166 (30%)	0.34 [0.13,0.87]	0.025

Third, participants were grouped into ever or never having TFV detection in plasma during follow-up. We compared the HIV incidence between participants with drug ever detected and those never having detectable drug using a Poisson regression model with the follow-up time as the offset. Case-cohort sampling was accounted for by the inverse-probability weighting method. The probability of being ever detected during follow-up depends on the number of samples available, and seroconverters generally have shorter follow-up, less samples, and thus have less of a chance to have a visit with detectable drug. We adjusted for the number of plasma samples in the Poisson model, in addition to the four confounding variables previously listed. Participants who did not have any data available on plasma TFV detection after imputation were deleted in this analysis. The results are shown in Table S6C.

Table S6C. HIV Incidence between Participants with Drug Ever Detected and Participants Never Having Detectable Drug in Plasma Samples using a Poisson Regression Model with Follow-Up Time as the Offset

	No. of sero-converters deleted due to no PK data	No. (%) women ever having TFV detection in plasma samples		Ever having detectable drug (Poisson regression) Adjusted RR [95% CI]	p-value
		Seroconverters	Seronegative		
TDF/FTC	0	24/61 (39%)	77/148 (52%)	0.83 [0.39,1.76]	0.624
TDF	6	14/54 (26%)	68/156 (44%)	0.55 [0.26,1.14]	0.107
1% TFV gel	5	15/56 (27%)	83/173 (48%)	0.43 [0.20,0.92]	0.029

Finally, for the vaginal gel arm, vaginal swab samples were available primarily for the month six and month twelve visits. The association of TFV detection in any of available swab samples with likelihood of HIV-1 seroconversion was assessed. A Cox model was fitted with an indicator variable for any TFV swab detection among the available swab samples for those in the case-cohort. Seroconverters who either seroconverted before swab data collection, or did not have any swab data were omitted in this analysis (Table S6D).

Table S6D. Association of TFV Detection in Any of Available Swab Samples with Likelihood of HIV-1 Seroconversion using a Cox Regression Model

	No. of seroconverters deleted due to no swab data	% women having TFV detection in swab		Any detection of drug on swab (Cox regression) Hazard Ratio [95% CI]	p-value
		Seroconverters	Seronegative		
1% TFV gel	24	15/37 =41%	84/170=49%	1.03 [0.47,2.25]	0.94

In summary, although TFV detection in vaginal fluid is higher than that in plasma, vaginal swab samples at month 6 and 12

did not significantly correlate with HIV seroconversion, most likely because a substantial number of seroconverters did not have swab data and detection of TFV on a swab is not very sensitive to recently missed doses because TFV can be detected on the swab long after a dose, longer than TFV detection in plasma after either an oral or vaginal dose. Hence, detection of TFV on a swab is not as good a marker of recent consistent use of gel as detection of drug in plasma is. Among the three ways we analyzed the relationship between TFV detection in plasma and HIV acquisition, two rough grouping rules for adherence lead to an association between TFV detection and risk of HIV acquisition in the gel arm, but we did not see such an association in the time-varying Cox regression model. Combined with adherence data presented in the main text, these results suggest that product use in the MTN-003 trial was low and intermittent, rendering it difficult to precisely align the time a product was taken and when HIV infection occurred. The time-varying Cox model is therefore most likely to be misclassifying the timing of exposure to drug and HIV infection time and thus is least sensitive for detection of an association. It is harder to detect TFV in plasma for participants in the gel arm because plasma drug concentration is far lower after vaginal compared to oral dosing which results in loss of detectable drug sooner after a dose with vaginal compared to oral dosing. Thus, any TFV detection in plasma at the first quarterly visit or at any time during follow-up may provide a better classification rule between users and nonusers, because it is more sensitive to recent missed doses, which enabled our ability to detect the association between undetectable drug and seroconversion observed in the gel arm for these two analyses (See Figure 1).

Table S6E. Characteristics associated with plasma TFV detection among participants in active product arms and with HIV incidence in participants in the placebo arms

	Plasma TFV[1] Detection among Participants in the Three Active Product Arms		HIV Infection among Participants in the Two Placebo Arms	
Characteristic	**Oral Arms Adjusted OR[2] (95% CI)**	**Gel Arm Adjusted OR[2] (95% CI)**	**Adjusted HR (95% CI)**	**P value**
Age >25 years	2.17 (1.36, 3.47)	0.99 (0.56, 1.76)	0.35 (0.22, 0.54)	<0.001
Married	2.96 (1.04, 8.38)	1.49 (0.54, 4.11)	0.12 (0.04, 0.41)	<0.001
Having more than one child	2.03 (1.24, 3.33)	1.45 (0.84, 2.51)	0.44 (0.28, 0.67)	0.0002
Independent income	1.78 (1.08, 2.93)	1.03 (0.60, 1.76)	0.63 (0.44, 0.91)	0.01

[1] TFV denotes tenofovir; OR odds ratio; HR hazard ratio; CI confidence interval.

[2] OR adjusted for study site, age, marital status, independent income, and multiparity.

Table S7. Safety and Adverse Effect Profiles: Summary

	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Participants Enrolled	5029	1007	1003	1009	1007	1003
Participants With One or More SAE[1]	181 (4%)	17 (2%)	42 (4%)	57 (6%)	39 (4%)	26 (3%)
Total Number of SAEs	203	17	43	68	45	30
Related	8 (4%)	0 (0%)	3 (7%)	4 (6%)	1 (2%)	0 (0%)
Not Related	195 (96%)	17 (100%)	40 (93%)	64 (94%)	44 (98%)	30 (100%)
Deaths	6 (<1%)	0 (0%)	0 (0%)	3 (<1%)	2 (<1%)	1 (<1%)
Related	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Related	6 (100%)	0 (0%)	0 (0%)	3 (100%)	2 (100%)	1 (100%)
Participants With One or More Grade 4 Event	60 (1%)	4 (<1%)	14 (1%)	17 (2%)	18 (2%)	7 (1%)
Total Number of Grade 4 Events	65	4	15	19	20	7
Related	6 (9%)	0 (0%)	3 (20%)	3 (16%)	0 (0%)	0 (0%)
Not Related	59 (91%)	4 (100%)	12 (80%)	16 (84%)	20 (100%)	7 (100%)
Participants With One or More Grade 3 Event	454 (9%)	81 (8%)	105 (10%)	96 (10%)	74 (7%)	98 (10%)
Total Number of Grade 3 Events	536	96	125	116	89	110
Related	136 (25%)	42 (44%)	39 (31%)	37 (32%)	6 (7%)	12 (11%)
Not Related	400 (75%)	54 (56%)	86 (69%)	79 (68%)	83 (93%)	98 (89%)
Participants With One or More Creatinine Event	31 (0.6%)	4 (0.4%)	13 (1.3%)	2 (0.2%)	9 (0.9%)	3 (0.3%)
Total Number of Creatinine Events	38	5	16	2	12	3
Related	26 (68%)	4 (80%)	15 (94%)	2 (100%)	4 (33%)	1 (33%)
Not Related	12 (32%)	1 (20%)	1 (6%)	0 (0%)	8 (67%)	2 (67%)

Table S7A. Severity Grade 2 or Higher Adverse Experiences by Severity: TDF

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Participants Enrolled	1007	--	--	--	--
Participants With One or More AE	489 (49%)	405 (40%)	80 (8%)	4 (<1%)	--
Blood and lymphatic system disorders	15 (1%)	12 (1%)	3 (<1%)	--	--
Anaemia	4 (<1%)	3 (<1%)	1 (<1%)	--	--
Normochromic normocytic anaemia	4 (<1%)	4 (<1%)	--	--	--
Hypochromic anaemia	2 (<1%)	2 (<1%)	--	--	--
Lymphopenia	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Neutropenia	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Iron deficiency anaemia	1 (<1%)	1 (<1%)	--	--	--
Congenital, familial and genetic disorders	1 (<1%)	1 (<1%)	--	--	--
Congenital anomaly in offspring	1 (<1%)	1 (<1%)	--	--	--
Gastrointestinal disorders	41 (4%)	41 (4%)	--	--	--
Nausea	13 (1%)	13 (1%)	--	--	--
Diarrhoea	12 (1%)	12 (1%)	--	--	--
Abdominal pain	9 (1%)	9 (1%)	--	--	--
Vomiting	6 (1%)	6 (1%)	--	--	--
Abdominal pain upper	3 (<1%)	3 (<1%)	--	--	--
Peptic ulcer	2 (<1%)	2 (<1%)	--	--	--
Abdominal pain lower	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Gastritis	1 (<1%)	1 (<1%)	--	--	--
General disorders and administration site conditions	5 (<1%)	2 (<1%)	3 (<1%)	--	--
Fatigue	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Oedema peripheral	2 (<1%)	--	2 (<1%)	--	--
Asthenia	1 (<1%)	--	1 (<1%)	--	--
Pain	1 (<1%)	--	1 (<1%)	--	--
Infections and infestations	252 (25%)	247 (25%)	5 (<1%)	--	--
Genitourinary chlamydia infection	105 (10%)	105 (10%)	--	--	--
Vulvovaginitis trichomonal	62 (6%)	62 (6%)	--	--	--
Genitourinary tract gonococcal infection	26 (3%)	26 (3%)	--	--	--
Vaginitis bacterial	25 (2%)	25 (2%)	--	--	--
Syphilis	15 (1%)	15 (1%)	--	--	--
Vulvovaginal candidiasis	14 (1%)	14 (1%)	--	--	--
Chlamydial infection	13 (1%)	13 (1%)	--	--	--
Gastroenteritis	8 (1%)	8 (1%)	--	--	--
Urinary tract infection	8 (1%)	8 (1%)	--	--	--
Pelvic inflammatory disease	6 (1%)	6 (1%)	--	--	--
Gonorrhoea	4 (<1%)	4 (<1%)	--	--	--
Cervicitis	3 (<1%)	3 (<1%)	--	--	--
Vulvovaginitis	3 (<1%)	3 (<1%)	--	--	--
Acute tonsillitis	2 (<1%)	2 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Bartholin's abscess	2 (<1%)	2 (<1%)	--	--	--
Escherichia urinary tract infection	2 (<1%)	2 (<1%)	--	--	--
Rash pustular	2 (<1%)	2 (<1%)	--	--	--
Tinea versicolour	2 (<1%)	2 (<1%)	--	--	--
Urogenital trichomoniasis	2 (<1%)	2 (<1%)	--	--	--
Vulval abscess	2 (<1%)	2 (<1%)	--	--	--
Carbuncle	1 (<1%)	1 (<1%)	--	--	--
Cystitis	1 (<1%)	1 (<1%)	--	--	--
Endometritis	1 (<1%)	1 (<1%)	--	--	--
Fungal skin infection	1 (<1%)	1 (<1%)	--	--	--
Gastroenteritis bacterial	1 (<1%)	--	1 (<1%)	--	--
Genital infection fungal	1 (<1%)	1 (<1%)	--	--	--
Herpes zoster	1 (<1%)	1 (<1%)	--	--	--
Influenza	1 (<1%)	1 (<1%)	--	--	--
Malaria	1 (<1%)	1 (<1%)	--	--	--
Postoperative wound infection	1 (<1%)	--	1 (<1%)	--	--
Postpartum sepsis	1 (<1%)	1 (<1%)	--	--	--
Pulmonary tuberculosis	1 (<1%)	--	1 (<1%)	--	--
Sinusitis	1 (<1%)	--	1 (<1%)	--	--
Staphylococcal infection	1 (<1%)	--	1 (<1%)	--	--
Injury, poisoning and procedural complications	10 (1%)	4 (<1%)	3 (<1%)	3 (<1%)	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Lower limb fracture	2 (<1%)	--	1 (<1%)	1 (<1%)	--
Ankle fracture	1 (<1%)	--	--	1 (<1%)	--
Induced abortion haemorrhage	1 (<1%)	1 (<1%)	--	--	--
Laceration	1 (<1%)	--	1 (<1%)	--	--
Ligament sprain	1 (<1%)	1 (<1%)	--	--	--
Procedural nausea	1 (<1%)	1 (<1%)	--	--	--
Thermal burn	1 (<1%)	--	1 (<1%)	--	--
Upper limb fracture	1 (<1%)	--	--	1 (<1%)	--
Vulvovaginal injury	1 (<1%)	1 (<1%)	--	--	--
Investigations	67 (7%)	56 (6%)	11 (1%)	--	--
Alanine aminotransferase increased	25 (2%)	19 (2%)	6 (1%)	--	--
Blood phosphorus decreased	20 (2%)	19 (2%)	1 (<1%)	--	--
Aspartate aminotransferase increased	16 (2%)	13 (1%)	3 (<1%)	--	--
Bone density decreased	7 (1%)	7 (1%)	--	--	--
Chlamydia test positive	3 (<1%)	3 (<1%)	--	--	--
Haemoglobin decreased	3 (<1%)	3 (<1%)	--	--	--
Neutrophil count decreased	3 (<1%)	3 (<1%)	--	--	--
Blood creatinine increased	1 (<1%)	1 (<1%)	--	--	--
Blood pressure increased	1 (<1%)	--	1 (<1%)	--	--
Enterobacter test positive	1 (<1%)	1 (<1%)	--	--	--
Klebsiella test positive	1 (<1%)	1 (<1%)	--	--	--
Neisseria test positive	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Treponema test positive	1 (<1%)	1 (<1%)	--	--	--
Metabolism and nutrition disorders	158 (16%)	113 (11%)	45 (4%)	--	--
Hypophosphataemia	134 (13%)	111 (11%)	23 (2%)	--	--
Abnormal loss of weight	21 (2%)	3 (<1%)	18 (2%)	--	--
Diabetes mellitus	4 (<1%)	--	4 (<1%)	--	--
Decreased appetite	2 (<1%)	2 (<1%)	--	--	--
Hyperglycaemia	1 (<1%)	--	1 (<1%)	--	--
Musculoskeletal and connective tissue disorders	2 (<1%)	--	2 (<1%)	--	--
Arthralgia	1 (<1%)	--	1 (<1%)	--	--
Back pain	1 (<1%)	--	1 (<1%)	--	--
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (<1%)	2 (<1%)	--	--	--
Vulvovaginal human papilloma virus infection	2 (<1%)	2 (<1%)	--	--	--
Nervous system disorders	42 (4%)	38 (4%)	4 (<1%)	--	--
Headache	33 (3%)	31 (3%)	2 (<1%)	--	--
Dizziness	6 (1%)	6 (1%)	--	--	--
Syncope	2 (<1%)	2 (<1%)	--	--	--
Carpal tunnel syndrome	1 (<1%)	1 (<1%)	--	--	--
Cerebral infarction	1 (<1%)	--	1 (<1%)	--	--
Meningism	1 (<1%)	--	1 (<1%)	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Pregnancy, puerperium and perinatal conditions	8 (1%)	5 (<1%)	3 (<1%)	--	--
Haemorrhage in pregnancy	5 (<1%)	4 (<1%)	1 (<1%)	--	--
Post abortion haemorrhage	2 (<1%)	--	2 (<1%)	--	--
Gestational hypertension	1 (<1%)	1 (<1%)	--	--	--
Renal and urinary disorders	46 (5%)	44 (4%)	2 (<1%)	--	--
Proteinuria	28 (3%)	27 (3%)	1 (<1%)	--	--
Dysuria	9 (1%)	9 (1%)	--	--	--
Glycosuria	6 (1%)	5 (<1%)	1 (<1%)	--	--
Haematuria	3 (<1%)	3 (<1%)	--	--	--
Pollakiuria	1 (<1%)	1 (<1%)	--	--	--
Reproductive system and breast disorders	45 (4%)	43 (4%)	2 (<1%)	--	--
Vaginal discharge	9 (1%)	9 (1%)	--	--	--
Cervical dysplasia	8 (1%)	7 (1%)	1 (<1%)	--	--
Pelvic pain	7 (1%)	6 (1%)	1 (<1%)	--	--
Vulvovaginal pruritus	6 (1%)	6 (1%)	--	--	--
Menometrorrhagia	4 (<1%)	4 (<1%)	--	--	--
Cervix erythema	3 (<1%)	3 (<1%)	--	--	--
Vulvovaginal ulceration	3 (<1%)	3 (<1%)	--	--	--
Dyspareunia	2 (<1%)	2 (<1%)	--	--	--
Ovarian cyst	2 (<1%)	2 (<1%)	--	--	--
Cervical discharge	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Dysmenorrhoea	1 (<1%)	1 (<1%)	--	--	--
Menorrhagia	1 (<1%)	1 (<1%)	--	--	--
Metrorrhagia	1 (<1%)	1 (<1%)	--	--	--
Pruritus genital	1 (<1%)	1 (<1%)	--	--	--
Uterine cervix ulcer	1 (<1%)	1 (<1%)	--	--	--
Uterine pain	1 (<1%)	1 (<1%)	--	--	--
Skin and subcutaneous tissue disorders	13 (1%)	13 (1%)	--	--	--
Rash maculo-papular	3 (<1%)	3 (<1%)	--	--	--
Blister	2 (<1%)	2 (<1%)	--	--	--
Dermatitis allergic	2 (<1%)	2 (<1%)	--	--	--
Rash	2 (<1%)	2 (<1%)	--	--	--
Urticaria	2 (<1%)	2 (<1%)	--	--	--
Dermatitis	1 (<1%)	1 (<1%)	--	--	--
Rash macular	1 (<1%)	1 (<1%)	--	--	--
Vascular disorders	5 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	--
Hypertension	3 (<1%)	--	3 (<1%)	--	--
Deep vein thrombosis	1 (<1%)	--	--	1 (<1%)	--
Hypotension	1 (<1%)	1 (<1%)	--	--	--

Table S7B. Severity Grade 2 or Higher Adverse Experiences by Severity: TDF/FTC

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Participants Enrolled	1003	--	--	--	--
Participants With One or More AE	599 (60%)	487 (49%)	98 (10%)	14 (1%)	--
Blood and lymphatic system disorders	27 (3%)	16 (2%)	11 (1%)	--	--
Anaemia	6 (1%)	3 (<1%)	3 (<1%)	--	--
Normochromic normocytic anaemia	6 (1%)	5 (<1%)	1 (<1%)	--	--
Hypochromic anaemia	5 (<1%)	2 (<1%)	3 (<1%)	--	--
Anaemia of pregnancy	3 (<1%)	1 (<1%)	2 (<1%)	--	--
Microcytic anaemia	3 (<1%)	1 (<1%)	2 (<1%)	--	--
Neutropenia	3 (<1%)	3 (<1%)	--	--	--
Lymphadenopathy	1 (<1%)	1 (<1%)	--	--	--
Eye disorders	4 (<1%)	2 (<1%)	2 (<1%)	--	--
Keratoconus	1 (<1%)	--	1 (<1%)	--	--
Retinal detachment	1 (<1%)	--	1 (<1%)	--	--
Vision blurred	1 (<1%)	1 (<1%)	--	--	--
Visual acuity reduced	1 (<1%)	1 (<1%)	--	--	--
Gastrointestinal disorders	42 (4%)	39 (4%)	3 (<1%)	--	--
Diarrhoea	21 (2%)	18 (2%)	3 (<1%)	--	--
Nausea	8 (1%)	8 (1%)	--	--	--
Vomiting	6 (1%)	6 (1%)	--	--	--
Abdominal pain lower	3 (<1%)	3 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Abdominal pain	2 (<1%)	2 (<1%)	--	--	--
Abdominal pain upper	2 (<1%)	2 (<1%)	--	--	--
Gastrointestinal tract irritation	1 (<1%)	1 (<1%)	--	--	--
Peptic ulcer	1 (<1%)	1 (<1%)	--	--	--
General disorders and administration site conditions	4 (<1%)	2 (<1%)	2 (<1%)	--	--
Fatigue	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Local swelling	1 (<1%)	1 (<1%)	--	--	--
Pyrexia	1 (<1%)	--	1 (<1%)	--	--
Hepatobiliary disorders	1 (<1%)	1 (<1%)	--	--	--
Hepatitis alcoholic	1 (<1%)	1 (<1%)	--	--	--
Infections and infestations	326 (33%)	319 (32%)	7 (1%)	--	--
Genitourinary chlamydia infection	144 (14%)	144 (14%)	--	--	--
Vulvovaginitis trichomonal	65 (6%)	65 (6%)	--	--	--
Genitourinary tract gonococcal infection	46 (5%)	46 (5%)	--	--	--
Vaginitis bacterial	34 (3%)	34 (3%)	--	--	--
Vulvovaginal candidiasis	17 (2%)	17 (2%)	--	--	--
Chlamydial infection	16 (2%)	16 (2%)	--	--	--
Urinary tract infection	15 (1%)	15 (1%)	--	--	--
Syphilis	10 (1%)	10 (1%)	--	--	--
Urogenital trichomoniasis	8 (1%)	8 (1%)	--	--	--
Gastroenteritis	7 (1%)	6 (1%)	1 (<1%)	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Pelvic inflammatory disease	6 (1%)	6 (1%)	--	--	--
Cervicitis	5 (<1%)	5 (<1%)	--	--	--
Vaginal infection	5 (<1%)	5 (<1%)	--	--	--
Escherichia urinary tract infection	4 (<1%)	4 (<1%)	--	--	--
Vulvovaginitis	4 (<1%)	4 (<1%)	--	--	--
Cystitis	2 (<1%)	2 (<1%)	--	--	--
Dysentery	2 (<1%)	2 (<1%)	--	--	--
Folliculitis	2 (<1%)	2 (<1%)	--	--	--
Gonorrhoea	2 (<1%)	2 (<1%)	--	--	--
Malaria	2 (<1%)	2 (<1%)	--	--	--
Pulmonary tuberculosis	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Pyelonephritis	2 (<1%)	2 (<1%)	--	--	--
Sexually transmitted disease	2 (<1%)	2 (<1%)	--	--	--
Tuberculosis	2 (<1%)	--	2 (<1%)	--	--
Vaginitis chlamydial	2 (<1%)	2 (<1%)	--	--	--
Varicella	2 (<1%)	2 (<1%)	--	--	--
Acute tonsillitis	1 (<1%)	--	1 (<1%)	--	--
Bacteriuria	1 (<1%)	1 (<1%)	--	--	--
Diarrhoea infectious	1 (<1%)	1 (<1%)	--	--	--
Genital infection fungal	1 (<1%)	1 (<1%)	--	--	--
Meningitis bacterial	1 (<1%)	--	1 (<1%)	--	--
Papilloma viral infection	1 (<1%)	1 (<1%)	--	--	--
Post procedural infection	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Respiratory tract infection	1 (<1%)	--	1 (<1%)	--	--
Tinea versicolour	1 (<1%)	1 (<1%)	--	--	--
Tonsillitis	1 (<1%)	1 (<1%)	--	--	--
Vulval abscess	1 (<1%)	1 (<1%)	--	--	--
Wound sepsis	1 (<1%)	--	1 (<1%)	--	--
Injury, poisoning and procedural complications	20 (2%)	12 (1%)	6 (1%)	2 (<1%)	--
Joint dislocation	2 (<1%)	--	2 (<1%)	--	--
Overdose	2 (<1%)	1 (<1%)	--	1 (<1%)	--
Anaemia postoperative	1 (<1%)	--	1 (<1%)	--	--
Ankle fracture	1 (<1%)	1 (<1%)	--	--	--
Burns second degree	1 (<1%)	1 (<1%)	--	--	--
Chemical poisoning	1 (<1%)	1 (<1%)	--	--	--
Foot fracture	1 (<1%)	1 (<1%)	--	--	--
Foreign body	1 (<1%)	--	1 (<1%)	--	--
Injury	1 (<1%)	--	--	1 (<1%)	--
Laceration	1 (<1%)	1 (<1%)	--	--	--
Lower limb fracture	1 (<1%)	1 (<1%)	--	--	--
Post procedural diarrhoea	1 (<1%)	1 (<1%)	--	--	--
Procedural headache	1 (<1%)	1 (<1%)	--	--	--
Procedural nausea	1 (<1%)	1 (<1%)	--	--	--
Procedural pain	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Soft tissue injury	1 (<1%)	--	1 (<1%)	--	--
Tendon injury	1 (<1%)	--	1 (<1%)	--	--
Thermal burn	1 (<1%)	1 (<1%)	--	--	--
Investigations	83 (8%)	69 (7%)	13 (1%)	1 (<1%)	--
Alanine aminotransferase increased	27 (3%)	20 (2%)	6 (1%)	1 (<1%)	--
Blood phosphorus decreased	19 (2%)	17 (2%)	2 (<1%)	--	--
Aspartate aminotransferase increased	18 (2%)	16 (2%)	1 (<1%)	1 (<1%)	--
Bone density decreased	13 (1%)	13 (1%)	--	--	--
Haemoglobin decreased	8 (1%)	6 (1%)	2 (<1%)	--	--
Escherichia test positive	4 (<1%)	4 (<1%)	--	--	--
Neutrophil count decreased	4 (<1%)	2 (<1%)	2 (<1%)	--	--
Klebsiella test positive	2 (<1%)	2 (<1%)	--	--	--
Blood pressure increased	1 (<1%)	1 (<1%)	--	--	--
Blood pressure systolic increased	1 (<1%)	--	1 (<1%)	--	--
Lymphocyte count decreased	1 (<1%)	1 (<1%)	--	--	--
Platelet count decreased	1 (<1%)	1 (<1%)	--	--	--
Metabolism and nutrition disorders	169 (17%)	123 (12%)	44 (4%)	2 (<1%)	--
Hypophosphataemia	140 (14%)	123 (12%)	17 (2%)	--	--
Abnormal loss of weight	28 (3%)	1 (<1%)	25 (2%)	2 (<1%)	--
Diabetes mellitus	4 (<1%)	--	4 (<1%)	--	--
Hyperglycaemia	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Decreased appetite	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<1%)	1 (<1%)	--	--	--
Anogenital warts	1 (<1%)	1 (<1%)	--	--	--
Nervous system disorders	51 (5%)	45 (4%)	3 (<1%)	3 (<1%)	--
Headache	40 (4%)	37 (4%)	1 (<1%)	2 (<1%)	--
Dizziness	6 (1%)	6 (1%)	--	--	--
Migraine	4 (<1%)	4 (<1%)	--	--	--
Convulsion	1 (<1%)	--	1 (<1%)	--	--
Loss of consciousness	1 (<1%)	--	1 (<1%)	--	--
Meningism	1 (<1%)	--	--	1 (<1%)	--
Post-traumatic headache	1 (<1%)	1 (<1%)	--	--	--
Syncope	1 (<1%)	--	1 (<1%)	--	--
Transient ischaemic attack	1 (<1%)	--	1 (<1%)	--	--
Pregnancy, puerperium and perinatal conditions	20 (2%)	13 (1%)	5 (<1%)	2 (<1%)	--
Haemorrhage in pregnancy	10 (1%)	7 (1%)	2 (<1%)	1 (<1%)	--
Post abortion haemorrhage	6 (1%)	5 (<1%)	1 (<1%)	--	--
Premature labour	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Ectopic pregnancy	1 (<1%)	--	--	1 (<1%)	--
Hyperemesis gravidarum	1 (<1%)	--	1 (<1%)	--	--
Pre-eclampsia	1 (<1%)	--	1 (<1%)	--	--
Psychiatric disorders	6 (1%)	1 (<1%)	1 (<1%)	4 (<1%)	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Intentional self-injury	2 (<1%)	1 (<1%)	--	1 (<1%)	--
Suicide attempt	2 (<1%)	--	--	2 (<1%)	--
Bipolar disorder	1 (<1%)	--	1 (<1%)	--	--
Depression	1 (<1%)	--	1 (<1%)	--	--
Suicidal ideation	1 (<1%)	--	--	1 (<1%)	--
Renal and urinary disorders	54 (5%)	49 (5%)	5 (<1%)	--	--
Proteinuria	32 (3%)	30 (3%)	2 (<1%)	--	--
Dysuria	11 (1%)	11 (1%)	--	--	--
Glycosuria	8 (1%)	6 (1%)	2 (<1%)	--	--
Haematuria	6 (1%)	5 (<1%)	1 (<1%)	--	--
Pollakiuria	2 (<1%)	2 (<1%)	--	--	--
Reproductive system and breast disorders	77 (8%)	75 (7%)	2 (<1%)	--	--
Vaginal discharge	16 (2%)	16 (2%)	--	--	--
Cervical dysplasia	15 (1%)	15 (1%)	--	--	--
Dysmenorrhoea	10 (1%)	10 (1%)	--	--	--
Pelvic pain	8 (1%)	8 (1%)	--	--	--
Vulvovaginal pruritus	8 (1%)	8 (1%)	--	--	--
Vulval ulceration	7 (1%)	7 (1%)	--	--	--
Cervical friability	3 (<1%)	3 (<1%)	--	--	--
Menorrhagia	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Cervical discharge	2 (<1%)	2 (<1%)	--	--	--
Dyspareunia	2 (<1%)	2 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Genital ulceration	2 (<1%)	2 (<1%)	--	--	--
Menometrorrhagia	2 (<1%)	2 (<1%)	--	--	--
Metrorrhagia	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Vulvovaginal ulceration	2 (<1%)	2 (<1%)	--	--	--
Amenorrhoea	1 (<1%)	1 (<1%)	--	--	--
Bartholin's cyst	1 (<1%)	1 (<1%)	--	--	--
Breast mass	1 (<1%)	1 (<1%)	--	--	--
Cervix erythema	1 (<1%)	1 (<1%)	--	--	--
Perineal pain	1 (<1%)	1 (<1%)	--	--	--
Uterine pain	1 (<1%)	1 (<1%)	--	--	--
Vaginal ulceration	1 (<1%)	1 (<1%)	--	--	--
Respiratory, thoracic and mediastinal disorders	2 (<1%)	--	2 (<1%)	--	--
Asthma	2 (<1%)	--	2 (<1%)	--	--
Skin and subcutaneous tissue disorders	18 (2%)	18 (2%)	--	--	--
Blister	3 (<1%)	3 (<1%)	--	--	--
Dermatitis	2 (<1%)	2 (<1%)	--	--	--
Rash	2 (<1%)	2 (<1%)	--	--	--
Rash macular	2 (<1%)	2 (<1%)	--	--	--
Rash papular	2 (<1%)	2 (<1%)	--	--	--
Rash pruritic	2 (<1%)	2 (<1%)	--	--	--
Urticaria	2 (<1%)	2 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Dermatitis allergic	1 (<1%)	1 (<1%)	--	--	--
Exfoliative rash	1 (<1%)	1 (<1%)	--	--	--
Intertrigo	1 (<1%)	1 (<1%)	--	--	--
Rash maculo-papular	1 (<1%)	1 (<1%)	--	--	--
Rash morbilliform	1 (<1%)	1 (<1%)	--	--	--
Vascular disorders	6 (1%)	--	6 (1%)	--	--
Hypertension	5 (<1%)	--	5 (<1%)	--	--
Hypotension	1 (<1%)	--	1 (<1%)	--	--

Table S7C. Severity Grade 2 or Higher Adverse Experiences by Severity: Oral Placebo

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Participants Enrolled	1009	--	--	--	--
Participants With One or More AE	596 (59%)	488 (48%)	88 (9%)	17 (2%)	3 (<1%)
Blood and lymphatic system disorders	28 (3%)	19 (2%)	9 (1%)	--	--
Anaemia	9 (1%)	8 (1%)	1 (<1%)	--	--
Neutropenia	6 (1%)	4 (<1%)	2 (<1%)	--	--
Anaemia of pregnancy	5 (<1%)	3 (<1%)	2 (<1%)	--	--
Microcytic anaemia	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Normochromic normocytic anaemia	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Thrombocytopenia	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Iron deficiency anaemia	1 (<1%)	1 (<1%)	--	--	--
Lymph node pain	1 (<1%)	--	1 (<1%)	--	--
Gastrointestinal disorders	53 (5%)	46 (5%)	6 (1%)	1 (<1%)	--
Diarrhoea	21 (2%)	19 (2%)	2 (<1%)	--	--
Nausea	15 (1%)	14 (1%)	1 (<1%)	--	--
Vomiting	9 (1%)	8 (1%)	1 (<1%)	--	--
Abdominal pain	7 (1%)	6 (1%)	--	1 (<1%)	--
Abdominal pain upper	4 (<1%)	4 (<1%)	--	--	--
Gastritis	4 (<1%)	3 (<1%)	1 (<1%)	--	--
Gastrooesophageal reflux disease	2 (<1%)	2 (<1%)	--	--	--
Abdominal pain lower	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Diarrhoea haemorrhagic	1 (<1%)	--	1 (<1%)	--	--
Gastric ulcer	1 (<1%)	--	1 (<1%)	--	--
Peptic ulcer	1 (<1%)	1 (<1%)	--	--	--
Umbilical hernia	1 (<1%)	--	1 (<1%)	--	--
General disorders and administration site conditions	3 (<1%)	--	3 (<1%)	--	--
Asthenia	1 (<1%)	--	1 (<1%)	--	--
Chest pain	1 (<1%)	--	1 (<1%)	--	--
Pyrexia	1 (<1%)	--	1 (<1%)	--	--
Hepatobiliary disorders	1 (<1%)	--	1 (<1%)	--	--
Cholecystitis	1 (<1%)	--	1 (<1%)	--	--
Infections and infestations	324 (32%)	307 (30%)	14 (1%)	3 (<1%)	--
Genitourinary chlamydia infection	154 (15%)	153 (15%)	1 (<1%)	--	--
Vulvovaginitis trichomonal	66 (7%)	66 (7%)	--	--	--
Genitourinary tract gonococcal infection	45 (4%)	45 (4%)	--	--	--
Vaginitis bacterial	29 (3%)	29 (3%)	--	--	--
Urinary tract infection	19 (2%)	19 (2%)	--	--	--
Chlamydial infection	15 (1%)	15 (1%)	--	--	--
Syphilis	15 (1%)	15 (1%)	--	--	--
Vulvovaginal candidiasis	13 (1%)	13 (1%)	--	--	--
Gastroenteritis	12 (1%)	9 (1%)	2 (<1%)	1 (<1%)	--
Urogenital trichomoniasis	12 (1%)	12 (1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Pelvic inflammatory disease	9 (1%)	8 (1%)	--	1 (<1%)	--
Vulval abscess	5 (<1%)	4 (<1%)	1 (<1%)	--	--
Vulvovaginitis	5 (<1%)	5 (<1%)	--	--	--
Escherichia urinary tract infection	4 (<1%)	4 (<1%)	--	--	--
Bartholin's abscess	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Pulmonary tuberculosis	3 (<1%)	--	3 (<1%)	--	--
Appendicitis	2 (<1%)	--	2 (<1%)	--	--
Body tinea	2 (<1%)	2 (<1%)	--	--	--
Cervicitis	2 (<1%)	2 (<1%)	--	--	--
Malaria	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Vaginal abscess	2 (<1%)	2 (<1%)	--	--	--
Vaginal infection	2 (<1%)	2 (<1%)	--	--	--
Abdominal wall abscess	1 (<1%)	--	1 (<1%)	--	--
Bacteriuria	1 (<1%)	1 (<1%)	--	--	--
Escherichia infection	1 (<1%)	1 (<1%)	--	--	--
Gastroenteritis shigella	1 (<1%)	1 (<1%)	--	--	--
Gingival abscess	1 (<1%)	--	1 (<1%)	--	--
Hepatitis B	1 (<1%)	1 (<1%)	--	--	--
Herpes zoster	1 (<1%)	1 (<1%)	--	--	--
Kidney infection	1 (<1%)	1 (<1%)	--	--	--
Pericarditis tuberculous	1 (<1%)	--	--	1 (<1%)	--
Pneumonia	1 (<1%)	1 (<1%)	--	--	--
Sexually transmitted disease	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Sinusitis	1 (<1%)	1 (<1%)	--	--	--
Subcutaneous abscess	1 (<1%)	1 (<1%)	--	--	--
Tonsillitis	1 (<1%)	--	1 (<1%)	--	--
Upper respiratory tract infection	1 (<1%)	1 (<1%)	--	--	--
Vaginitis chlamydial	1 (<1%)	1 (<1%)	--	--	--
Viraemia	1 (<1%)	1 (<1%)	--	--	--
Injury, poisoning and procedural complications	19 (2%)	12 (1%)	4 (<1%)	1 (<1%)	2 (<1%)
Procedural nausea	2 (<1%)	2 (<1%)	--	--	--
Procedural pain	2 (<1%)	2 (<1%)	--	--	--
Procedural vomiting	2 (<1%)	2 (<1%)	--	--	--
Thermal burn	2 (<1%)	--	2 (<1%)	--	--
Ankle fracture	1 (<1%)	--	1 (<1%)	--	--
Arthropod bite	1 (<1%)	1 (<1%)	--	--	--
Head injury	1 (<1%)	1 (<1%)	--	--	--
Injury	1 (<1%)	--	--	--	1 (<1%)
Internal injury	1 (<1%)	--	--	--	1 (<1%)
Laceration	1 (<1%)	1 (<1%)	--	--	--
Pelvic fracture	1 (<1%)	--	1 (<1%)	--	--
Perineal injury	1 (<1%)	1 (<1%)	--	--	--
Post procedural discharge	1 (<1%)	1 (<1%)	--	--	--
Post procedural haemorrhage	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Post-traumatic pain	1 (<1%)	1 (<1%)	--	--	--
Stab wound	1 (<1%)	--	--	1 (<1%)	--
Investigations	81 (8%)	67 (7%)	11 (1%)	3 (<1%)	--
Alanine aminotransferase increased	30 (3%)	23 (2%)	4 (<1%)	3 (<1%)	--
Blood phosphorus decreased	20 (2%)	18 (2%)	2 (<1%)	--	--
Aspartate aminotransferase increased	12 (1%)	11 (1%)	1 (<1%)	--	--
Haemoglobin decreased	12 (1%)	9 (1%)	3 (<1%)	--	--
Bone density decreased	10 (1%)	10 (1%)	--	--	--
Blood pressure increased	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Enterococcus test positive	2 (<1%)	2 (<1%)	--	--	--
Neutrophil count decreased	2 (<1%)	2 (<1%)	--	--	--
Blood glucose increased	1 (<1%)	1 (<1%)	--	--	--
Escherichia test positive	1 (<1%)	1 (<1%)	--	--	--
Klebsiella test positive	1 (<1%)	1 (<1%)	--	--	--
Lymphocyte count decreased	1 (<1%)	--	1 (<1%)	--	--
Platelet count decreased	1 (<1%)	1 (<1%)	--	--	--
Streptococcus test positive	1 (<1%)	1 (<1%)	--	--	--
Urine output decreased	1 (<1%)	1 (<1%)	--	--	--
Metabolism and nutrition disorders	155 (15%)	129 (13%)	26 (3%)	--	--
Hypophosphataemia	139 (14%)	129 (13%)	10 (1%)	--	--
Abnormal loss of weight	17 (2%)	3 (<1%)	14 (1%)	--	--
Decreased appetite	2 (<1%)	1 (<1%)	1 (<1%)	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Diabetes mellitus	2 (<1%)	--	2 (<1%)	--	--
Hyperglycaemia	1 (<1%)	1 (<1%)	--	--	--
Musculoskeletal and connective tissue disorders	1 (<1%)	--	1 (<1%)	--	--
Arthralgia	1 (<1%)	--	1 (<1%)	--	--
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (<1%)	1 (<1%)	1 (<1%)	--	1 (<1%)
Anogenital warts	1 (<1%)	1 (<1%)	--	--	--
Gliomatosis cerebri	1 (<1%)	--	--	--	1 (<1%)
Lipoma	1 (<1%)	--	1 (<1%)	--	--
Nervous system disorders	55 (5%)	51 (5%)	4 (<1%)	--	--
Headache	45 (4%)	44 (4%)	1 (<1%)	--	--
Dizziness	4 (<1%)	4 (<1%)	--	--	--
Cerebrovascular accident	1 (<1%)	1 (<1%)	--	--	--
Epilepsy	1 (<1%)	--	1 (<1%)	--	--
Migraine	1 (<1%)	--	1 (<1%)	--	--
Post-traumatic headache	1 (<1%)	1 (<1%)	--	--	--
Tension headache	1 (<1%)	1 (<1%)	--	--	--
Transient ischaemic attack	1 (<1%)	--	1 (<1%)	--	--
Pregnancy, puerperium and perinatal conditions	18 (2%)	5 (<1%)	7 (1%)	6 (1%)	--
Haemorrhage in pregnancy	6 (1%)	1 (<1%)	4 (<1%)	1 (<1%)	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Post abortion haemorrhage	5 (<1%)	3 (<1%)	2 (<1%)	--	--
Premature labour	5 (<1%)	--	--	5 (<1%)	--
Premature rupture of membranes	2 (<1%)	--	1 (<1%)	1 (<1%)	--
Retained products of conception	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Ectopic pregnancy	1 (<1%)	--	--	1 (<1%)	--
Intrapartum haemorrhage	1 (<1%)	--	1 (<1%)	--	--
Vomiting in pregnancy	1 (<1%)	1 (<1%)	--	--	--
Psychiatric disorders	4 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	--
Suicide attempt	2 (<1%)	--	--	2 (<1%)	--
Depression suicidal	1 (<1%)	--	1 (<1%)	--	--
Schizophrenia	1 (<1%)	1 (<1%)	--	--	--
Renal and urinary disorders	55 (5%)	53 (5%)	2 (<1%)	--	--
Proteinuria	35 (3%)	34 (3%)	1 (<1%)	--	--
Dysuria	13 (1%)	13 (1%)	--	--	--
Pollakiuria	5 (<1%)	5 (<1%)	--	--	--
Glycosuria	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Micturition urgency	2 (<1%)	2 (<1%)	--	--	--
Bladder pain	1 (<1%)	1 (<1%)	--	--	--
Haematuria	1 (<1%)	1 (<1%)	--	--	--
Nephritis	1 (<1%)	1 (<1%)	--	--	--
Pyuria	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Reproductive system and breast disorders	85 (8%)	83 (8%)	2 (<1%)	--	--
Cervical dysplasia	23 (2%)	23 (2%)	--	--	--
Vaginal discharge	17 (2%)	17 (2%)	--	--	--
Pelvic pain	9 (1%)	9 (1%)	--	--	--
Vulvovaginal pruritus	8 (1%)	8 (1%)	--	--	--
Metrorrhagia	6 (1%)	5 (<1%)	1 (<1%)	--	--
Vulval ulceration	6 (1%)	6 (1%)	--	--	--
Dysmenorrhoea	5 (<1%)	5 (<1%)	--	--	--
Menorrhagia	4 (<1%)	4 (<1%)	--	--	--
Bartholin's cyst	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Cervix erythema	3 (<1%)	3 (<1%)	--	--	--
Dyspareunia	3 (<1%)	3 (<1%)	--	--	--
Vulvovaginal burning sensation	2 (<1%)	2 (<1%)	--	--	--
Breast pain	1 (<1%)	1 (<1%)	--	--	--
Cervical discharge	1 (<1%)	1 (<1%)	--	--	--
Coital bleeding	1 (<1%)	1 (<1%)	--	--	--
Fallopian tube cyst	1 (<1%)	1 (<1%)	--	--	--
Genital burning sensation	1 (<1%)	1 (<1%)	--	--	--
Genital ulceration	1 (<1%)	1 (<1%)	--	--	--
Menometrorrhagia	1 (<1%)	1 (<1%)	--	--	--
Pruritus genital	1 (<1%)	1 (<1%)	--	--	--
Vaginal odour	1 (<1%)	1 (<1%)	--	--	--
Vulvovaginal rash	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Vulvovaginal ulceration	1 (<1%)	1 (<1%)	--	--	--
Respiratory, thoracic and mediastinal disorders	4 (<1%)	--	4 (<1%)	--	--
Asthma	2 (<1%)	--	2 (<1%)	--	--
Dyspnoea	1 (<1%)	--	1 (<1%)	--	--
Epistaxis	1 (<1%)	--	1 (<1%)	--	--
Skin and subcutaneous tissue disorders	19 (2%)	19 (2%)	--	--	--
Blister	2 (<1%)	2 (<1%)	--	--	--
Pruritus	2 (<1%)	2 (<1%)	--	--	--
Rash	2 (<1%)	2 (<1%)	--	--	--
Rash generalised	2 (<1%)	2 (<1%)	--	--	--
Rash macular	2 (<1%)	2 (<1%)	--	--	--
Rash maculo-papular	2 (<1%)	2 (<1%)	--	--	--
Dermatitis	1 (<1%)	1 (<1%)	--	--	--
Dermatitis contact	1 (<1%)	1 (<1%)	--	--	--
Drug eruption	1 (<1%)	1 (<1%)	--	--	--
Eczema	1 (<1%)	1 (<1%)	--	--	--
Papule	1 (<1%)	1 (<1%)	--	--	--
Rash erythematous	1 (<1%)	1 (<1%)	--	--	--
Rash papular	1 (<1%)	1 (<1%)	--	--	--
Rash pruritic	1 (<1%)	1 (<1%)	--	--	--
Vascular disorders	5 (<1%)	--	4 (<1%)	1 (<1%)	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Hypertension	5 (<1%)	--	4 (<1%)	1 (<1%)	--

Table S7D. Severity Grade 2 or Higher Adverse Experiences by Severity: Tenofovir Gel

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Participants Enrolled	1007	--	--	--	--
Participants With One or More AE	527 (52%)	443 (44%)	65 (6%)	17 (2%)	2 (<1%)
Blood and lymphatic system disorders	19 (2%)	16 (2%)	3 (<1%)	--	--
Anaemia	7 (1%)	5 (<1%)	2 (<1%)	--	--
Anaemia of pregnancy	5 (<1%)	4 (<1%)	1 (<1%)	--	--
Hypochromic anaemia	4 (<1%)	4 (<1%)	--	--	--
Lymphopenia	1 (<1%)	1 (<1%)	--	--	--
Neutropenia	1 (<1%)	1 (<1%)	--	--	--
Normochromic normocytic anaemia	1 (<1%)	1 (<1%)	--	--	--
Congenital, familial and genetic disorders	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Congenital anomaly in offspring	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Gastrointestinal disorders	28 (3%)	25 (2%)	2 (<1%)	1 (<1%)	--
Diarrhoea	11 (1%)	10 (1%)	1 (<1%)	--	--
Abdominal pain	8 (1%)	8 (1%)	--	--	--
Vomiting	4 (<1%)	3 (<1%)	1 (<1%)	--	--
Peptic ulcer	3 (<1%)	3 (<1%)	--	--	--
Nausea	2 (<1%)	2 (<1%)	--	--	--
Abdominal pain lower	1 (<1%)	1 (<1%)	--	--	--
Abdominal pain upper	1 (<1%)	--	--	1 (<1%)	--
Dyspepsia	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Gastrooesophageal reflux disease	1 (<1%)	1 (<1%)	--	--	--
Irritable bowel syndrome	1 (<1%)	1 (<1%)	--	--	--
General disorders and administration site conditions	5 (<1%)	3 (<1%)	1 (<1%)	--	1 (<1%)
Fatigue	2 (<1%)	2 (<1%)	--	--	--
Suprapubic pain	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Death	1 (<1%)	--	--	--	1 (<1%)
Malaise	1 (<1%)	1 (<1%)	--	--	--
Hepatobiliary disorders	1 (<1%)	--	--	1 (<1%)	--
Cholecystitis	1 (<1%)	--	--	1 (<1%)	--
Immune system disorders	1 (<1%)	1 (<1%)	--	--	--
Food allergy	1 (<1%)	1 (<1%)	--	--	--
Infections and infestations	258 (26%)	250 (25%)	7 (1%)	1 (<1%)	--
Genitourinary chlamydia infection	100 (10%)	100 (10%)	--	--	--
Vulvovaginitis trichomonal	46 (5%)	46 (5%)	--	--	--
Genitourinary tract gonococcal infection	40 (4%)	40 (4%)	--	--	--
Vaginitis bacterial	27 (3%)	27 (3%)	--	--	--
Vulvovaginal candidiasis	21 (2%)	21 (2%)	--	--	--
Chlamydial infection	17 (2%)	17 (2%)	--	--	--
Pelvic inflammatory disease	9 (1%)	9 (1%)	--	--	--
Syphilis	9 (1%)	9 (1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Urinary tract infection	8 (1%)	8 (1%)	--	--	--
Gastroenteritis	6 (1%)	5 (<1%)	1 (<1%)	--	--
Gonorrhoea	6 (1%)	6 (1%)	--	--	--
Vulvovaginitis	4 (<1%)	4 (<1%)	--	--	--
Malaria	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Pulmonary tuberculosis	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Urogenital trichomoniasis	3 (<1%)	3 (<1%)	--	--	--
Bartholin's abscess	2 (<1%)	2 (<1%)	--	--	--
Breast abscess	2 (<1%)	2 (<1%)	--	--	--
Escherichia urinary tract infection	2 (<1%)	2 (<1%)	--	--	--
Sexually transmitted disease	2 (<1%)	2 (<1%)	--	--	--
Varicella	2 (<1%)	2 (<1%)	--	--	--
Appendicitis	1 (<1%)	--	1 (<1%)	--	--
Body tinea	1 (<1%)	1 (<1%)	--	--	--
Disseminated tuberculosis	1 (<1%)	--	1 (<1%)	--	--
Endometritis	1 (<1%)	1 (<1%)	--	--	--
Folliculitis	1 (<1%)	1 (<1%)	--	--	--
Groin abscess	1 (<1%)	1 (<1%)	--	--	--
Klebsiella infection	1 (<1%)	1 (<1%)	--	--	--
Mastitis	1 (<1%)	1 (<1%)	--	--	--
Meningitis	1 (<1%)	--	--	1 (<1%)	--
Otitis media	1 (<1%)	1 (<1%)	--	--	--
Post procedural sepsis	1 (<1%)	--	1 (<1%)	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Pyelonephritis	1 (<1%)	--	1 (<1%)	--	--
Salpingitis	1 (<1%)	1 (<1%)	--	--	--
Sinusitis	1 (<1%)	1 (<1%)	--	--	--
Skin infection	1 (<1%)	--	1 (<1%)	--	--
Tonsillitis	1 (<1%)	--	1 (<1%)	--	--
Vaginitis chlamydial	1 (<1%)	1 (<1%)	--	--	--
Vulval abscess	1 (<1%)	1 (<1%)	--	--	--
Injury, poisoning and procedural complications	11 (1%)	8 (1%)	1 (<1%)	1 (<1%)	1 (<1%)
Ankle fracture	2 (<1%)	2 (<1%)	--	--	--
Abdominal injury	1 (<1%)	1 (<1%)	--	--	--
Electric shock	1 (<1%)	--	--	1 (<1%)	--
Head injury	1 (<1%)	1 (<1%)	--	--	--
Induced abortion haemorrhage	1 (<1%)	1 (<1%)	--	--	--
Injury	1 (<1%)	--	1 (<1%)	--	--
Post procedural haemorrhage	1 (<1%)	1 (<1%)	--	--	--
Procedural pain	1 (<1%)	1 (<1%)	--	--	--
Thermal burn	1 (<1%)	--	--	--	1 (<1%)
Vulval laceration	1 (<1%)	1 (<1%)	--	--	--
Investigations	76 (8%)	66 (7%)	5 (<1%)	5 (<1%)	--
Alanine aminotransferase increased	30 (3%)	24 (2%)	1 (<1%)	5 (<1%)	--
Blood phosphorus decreased	29 (3%)	28 (3%)	1 (<1%)	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Aspartate aminotransferase increased	11 (1%)	9 (1%)	1 (<1%)	1 (<1%)	--
Haemoglobin decreased	9 (1%)	7 (1%)	2 (<1%)	--	--
Neutrophil count decreased	6 (1%)	5 (<1%)	1 (<1%)	--	--
Escherichia test positive	2 (<1%)	2 (<1%)	--	--	--
Candida test positive	1 (<1%)	1 (<1%)	--	--	--
Enterococcus test positive	1 (<1%)	1 (<1%)	--	--	--
Metabolism and nutrition disorders	173 (17%)	132 (13%)	38 (4%)	3 (<1%)	--
Hypophosphataemia	151 (15%)	129 (13%)	20 (2%)	2 (<1%)	--
Abnormal loss of weight	23 (2%)	4 (<1%)	18 (2%)	1 (<1%)	--
Diabetes mellitus	2 (<1%)	2 (<1%)	--	--	--
Decreased appetite	1 (<1%)	1 (<1%)	--	--	--
Musculoskeletal and connective tissue disorders	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Flank pain	1 (<1%)	1 (<1%)	--	--	--
Muscle spasms	1 (<1%)	1 (<1%)	--	--	--
Musculoskeletal chest pain	1 (<1%)	--	1 (<1%)	--	--
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<1%)	--	1 (<1%)	--	--
Uterine leiomyoma	1 (<1%)	--	1 (<1%)	--	--
Nervous system disorders	29 (3%)	24 (2%)	3 (<1%)	2 (<1%)	--
Headache	27 (3%)	23 (2%)	2 (<1%)	2 (<1%)	--
Dizziness	3 (<1%)	2 (<1%)	--	1 (<1%)	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Meningism	1 (<1%)	--	1 (<1%)	--	--
Syncope	1 (<1%)	--	1 (<1%)	--	--
Pregnancy, puerperium and perinatal conditions	11 (1%)	4 (<1%)	3 (<1%)	4 (<1%)	--
Haemorrhage in pregnancy	4 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	--
Post abortion haemorrhage	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	--
Premature labour	2 (<1%)	--	--	2 (<1%)	--
Ectopic pregnancy	1 (<1%)	--	1 (<1%)	--	--
Hyperemesis gravidarum	1 (<1%)	1 (<1%)	--	--	--
Postpartum haemorrhage	1 (<1%)	--	1 (<1%)	--	--
Vomiting in pregnancy	1 (<1%)	1 (<1%)	--	--	--
Psychiatric disorders	2 (<1%)	--	2 (<1%)	--	--
Confusional state	1 (<1%)	--	1 (<1%)	--	--
Depression	1 (<1%)	--	1 (<1%)	--	--
Renal and urinary disorders	52 (5%)	49 (5%)	3 (<1%)	--	--
Proteinuria	27 (3%)	27 (3%)	--	--	--
Dysuria	16 (2%)	16 (2%)	--	--	--
Glycosuria	6 (1%)	4 (<1%)	2 (<1%)	--	--
Pollakiuria	5 (<1%)	5 (<1%)	--	--	--
Haematuria	4 (<1%)	3 (<1%)	1 (<1%)	--	--
Bladder pain	1 (<1%)	1 (<1%)	--	--	--
Micturition urgency	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Reproductive system and breast disorders	78 (8%)	77 (8%)	1 (<1%)	--	--
Vaginal discharge	11 (1%)	11 (1%)	--	--	--
Metrorrhagia	9 (1%)	9 (1%)	--	--	--
Cervical dysplasia	7 (1%)	7 (1%)	--	--	--
Menorrhagia	7 (1%)	6 (1%)	1 (<1%)	--	--
Menometrorrhagia	6 (1%)	6 (1%)	--	--	--
Pelvic pain	6 (1%)	6 (1%)	--	--	--
Vulval ulceration	6 (1%)	6 (1%)	--	--	--
Dysmenorrhoea	5 (<1%)	5 (<1%)	--	--	--
Vulvovaginal pruritus	5 (<1%)	5 (<1%)	--	--	--
Cervical friability	3 (<1%)	3 (<1%)	--	--	--
Cervical discharge	2 (<1%)	2 (<1%)	--	--	--
Cervix erythema	2 (<1%)	2 (<1%)	--	--	--
Uterine pain	2 (<1%)	2 (<1%)	--	--	--
Vulvovaginal burning sensation	2 (<1%)	2 (<1%)	--	--	--
Vulvovaginal pain	2 (<1%)	2 (<1%)	--	--	--
Vulvovaginal ulceration	2 (<1%)	2 (<1%)	--	--	--
Adnexa uteri mass	1 (<1%)	1 (<1%)	--	--	--
Breast discharge	1 (<1%)	1 (<1%)	--	--	--
Breast engorgement	1 (<1%)	1 (<1%)	--	--	--
Breast enlargement	1 (<1%)	1 (<1%)	--	--	--
Breast pain	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Breast tenderness	1 (<1%)	1 (<1%)	--	--	--
Dyspareunia	1 (<1%)	1 (<1%)	--	--	--
Genital erosion	1 (<1%)	1 (<1%)	--	--	--
Genital ulceration	1 (<1%)	1 (<1%)	--	--	--
Menstrual disorder	1 (<1%)	1 (<1%)	--	--	--
Ovarian cyst	1 (<1%)	1 (<1%)	--	--	--
Pruritus genital	1 (<1%)	1 (<1%)	--	--	--
Vaginal disorder	1 (<1%)	1 (<1%)	--	--	--
Vaginal ulceration	1 (<1%)	1 (<1%)	--	--	--
Vulvar erosion	1 (<1%)	1 (<1%)	--	--	--
Vulvovaginal rash	1 (<1%)	1 (<1%)	--	--	--
Respiratory, thoracic and mediastinal disorders	1 (<1%)	--	1 (<1%)	--	--
Dyspnoea	1 (<1%)	--	1 (<1%)	--	--
Skin and subcutaneous tissue disorders	10 (1%)	10 (1%)	--	--	--
Blister	3 (<1%)	3 (<1%)	--	--	--
Rash	2 (<1%)	2 (<1%)	--	--	--
Dermatitis allergic	1 (<1%)	1 (<1%)	--	--	--
Dermatitis contact	1 (<1%)	1 (<1%)	--	--	--
Rash macular	1 (<1%)	1 (<1%)	--	--	--
Rash maculo-papular	1 (<1%)	1 (<1%)	--	--	--
Skin reaction	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Vascular disorders	5 (<1%)	--	5 (<1%)	--	--
Hypertension	4 (<1%)	--	4 (<1%)	--	--
Hypotension	1 (<1%)	--	1 (<1%)	--	--

Table S7E. Severity Grade 2 or Higher Adverse Experiences by Severity: Placebo Gel

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Participants Enrolled	1003	--	--	--	--
Participants With One or More AE	518 (52%)	415 (41%)	96 (10%)	6 (1%)	1 (<1%)
Blood and lymphatic system disorders	20 (2%)	14 (1%)	5 (<1%)	1 (<1%)	--
Neutropenia	5 (<1%)	4 (<1%)	1 (<1%)	--	--
Hypochromic anaemia	4 (<1%)	2 (<1%)	2 (<1%)	--	--
Normochromic normocytic anaemia	4 (<1%)	3 (<1%)	1 (<1%)	--	--
Anaemia	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	--
Anaemia of pregnancy	1 (<1%)	1 (<1%)	--	--	--
Iron deficiency anaemia	1 (<1%)	1 (<1%)	--	--	--
Lymphopenia	1 (<1%)	1 (<1%)	--	--	--
Thrombocytopenia	1 (<1%)	1 (<1%)	--	--	--
Congenital, familial and genetic disorders	1 (<1%)	--	1 (<1%)	--	--
Congenital anomaly in offspring	1 (<1%)	--	1 (<1%)	--	--
Gastrointestinal disorders	43 (4%)	37 (4%)	4 (<1%)	2 (<1%)	--
Diarrhoea	18 (2%)	17 (2%)	1 (<1%)	--	--
Abdominal pain	8 (1%)	7 (1%)	--	1 (<1%)	--
Abdominal pain lower	5 (<1%)	5 (<1%)	--	--	--
Nausea	4 (<1%)	3 (<1%)	1 (<1%)	--	--
Vomiting	4 (<1%)	2 (<1%)	2 (<1%)	--	--
Abdominal pain upper	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Abdominal tenderness	1 (<1%)	1 (<1%)	--	--	--
Food poisoning	1 (<1%)	--	--	1 (<1%)	--
Gastric ulcer	1 (<1%)	1 (<1%)	--	--	--
Gastritis	1 (<1%)	--	1 (<1%)	--	--
Haemorrhoids	1 (<1%)	1 (<1%)	--	--	--
Mouth ulceration	1 (<1%)	1 (<1%)	--	--	--
Peptic ulcer	1 (<1%)	1 (<1%)	--	--	--
General disorders and administration site conditions	1 (<1%)	1 (<1%)	--	--	--
Suprapubic pain	1 (<1%)	1 (<1%)	--	--	--
Immune system disorders	1 (<1%)	--	1 (<1%)	--	--
Hypersensitivity	1 (<1%)	--	1 (<1%)	--	--
Infections and infestations	273 (27%)	261 (26%)	11 (1%)	--	1 (<1%)
Genitourinary chlamydia infection	107 (11%)	107 (11%)	--	--	--
Vulvovaginitis trichomonal	55 (5%)	55 (5%)	--	--	--
Vaginitis bacterial	33 (3%)	33 (3%)	--	--	--
Genitourinary tract gonococcal infection	32 (3%)	32 (3%)	--	--	--
Urinary tract infection	19 (2%)	19 (2%)	--	--	--
Vulvovaginal candidiasis	14 (1%)	14 (1%)	--	--	--
Chlamydial infection	13 (1%)	13 (1%)	--	--	--
Syphilis	11 (1%)	11 (1%)	--	--	--
Pelvic inflammatory disease	8 (1%)	7 (1%)	1 (<1%)	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Cervicitis	7 (1%)	7 (1%)	--	--	--
Pulmonary tuberculosis	6 (1%)	3 (<1%)	2 (<1%)	--	1 (<1%)
Vulvovaginitis	6 (1%)	6 (1%)	--	--	--
Gastroenteritis	4 (<1%)	3 (<1%)	1 (<1%)	--	--
Herpes zoster	4 (<1%)	4 (<1%)	--	--	--
Vaginal infection	3 (<1%)	3 (<1%)	--	--	--
Vulval abscess	3 (<1%)	3 (<1%)	--	--	--
Dysentery	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Escherichia urinary tract infection	2 (<1%)	2 (<1%)	--	--	--
Folliculitis	2 (<1%)	2 (<1%)	--	--	--
Malaria	2 (<1%)	2 (<1%)	--	--	--
Rash pustular	2 (<1%)	2 (<1%)	--	--	--
Tinea versicolour	2 (<1%)	2 (<1%)	--	--	--
Acarodermatitis	1 (<1%)	1 (<1%)	--	--	--
Appendicitis	1 (<1%)	--	1 (<1%)	--	--
Body tinea	1 (<1%)	1 (<1%)	--	--	--
Breast abscess	1 (<1%)	1 (<1%)	--	--	--
Chancroid	1 (<1%)	1 (<1%)	--	--	--
Fungal skin infection	1 (<1%)	1 (<1%)	--	--	--
Gonorrhoea	1 (<1%)	1 (<1%)	--	--	--
Meningitis viral	1 (<1%)	--	1 (<1%)	--	--
Pyelonephritis	1 (<1%)	--	1 (<1%)	--	--
Respiratory tract infection	1 (<1%)	--	1 (<1%)	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Sinusitis	1 (<1%)	--	1 (<1%)	--	--
Subcutaneous abscess	1 (<1%)	1 (<1%)	--	--	--
Tinea cruris	1 (<1%)	1 (<1%)	--	--	--
Tinea infection	1 (<1%)	1 (<1%)	--	--	--
Tonsillitis	1 (<1%)	--	1 (<1%)	--	--
Urinary tract infection bacterial	1 (<1%)	1 (<1%)	--	--	--
Vaginitis chlamydial	1 (<1%)	1 (<1%)	--	--	--
Vulvitis	1 (<1%)	1 (<1%)	--	--	--
Injury, poisoning and procedural complications	4 (<1%)	4 (<1%)	--	--	--
Perineal injury	1 (<1%)	1 (<1%)	--	--	--
Procedural headache	1 (<1%)	1 (<1%)	--	--	--
Procedural pain	1 (<1%)	1 (<1%)	--	--	--
Wrist fracture	1 (<1%)	1 (<1%)	--	--	--
Investigations	55 (5%)	41 (4%)	13 (1%)	1 (<1%)	--
Alanine aminotransferase increased	17 (2%)	11 (1%)	6 (1%)	--	--
Blood phosphorus decreased	17 (2%)	17 (2%)	--	--	--
Aspartate aminotransferase increased	12 (1%)	9 (1%)	2 (<1%)	1 (<1%)	--
Haemoglobin decreased	7 (1%)	5 (<1%)	2 (<1%)	--	--
Neutrophil count decreased	5 (<1%)	4 (<1%)	1 (<1%)	--	--
Blood pressure increased	3 (<1%)	1 (<1%)	2 (<1%)	--	--
Chlamydia test positive	2 (<1%)	2 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Blood glucose increased	1 (<1%)	1 (<1%)	--	--	--
Blood pressure diastolic increased	1 (<1%)	--	1 (<1%)	--	--
Escherichia test positive	1 (<1%)	1 (<1%)	--	--	--
Hepatitis B surface antibody positive	1 (<1%)	1 (<1%)	--	--	--
Platelet count decreased	1 (<1%)	1 (<1%)	--	--	--
Urine output decreased	1 (<1%)	1 (<1%)	--	--	--
Metabolism and nutrition disorders	155 (15%)	103 (10%)	51 (5%)	1 (<1%)	--
Hypophosphataemia	122 (12%)	98 (10%)	24 (2%)	--	--
Abnormal loss of weight	29 (3%)	4 (<1%)	24 (2%)	1 (<1%)	--
Diabetes mellitus	4 (<1%)	1 (<1%)	3 (<1%)	--	--
Hyperglycaemia	1 (<1%)	--	1 (<1%)	--	--
Type 2 diabetes mellitus	1 (<1%)	--	1 (<1%)	--	--
Musculoskeletal and connective tissue disorders	6 (1%)	3 (<1%)	3 (<1%)	--	--
Back pain	3 (<1%)	2 (<1%)	1 (<1%)	--	--
Flank pain	1 (<1%)	1 (<1%)	--	--	--
Neck mass	1 (<1%)	--	1 (<1%)	--	--
Rheumatoid arthritis	1 (<1%)	--	1 (<1%)	--	--
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (<1%)	2 (<1%)	--	--	--
Cervicitis human papilloma virus	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Vulvovaginal human papilloma virus infection	1 (<1%)	1 (<1%)	--	--	--
Nervous system disorders	35 (3%)	33 (3%)	2 (<1%)	--	--
Headache	31 (3%)	30 (3%)	1 (<1%)	--	--
Dizziness	5 (<1%)	5 (<1%)	--	--	--
Optic neuritis	1 (<1%)	--	1 (<1%)	--	--
Pregnancy, puerperium and perinatal conditions	12 (1%)	5 (<1%)	6 (1%)	1 (<1%)	--
Haemorrhage in pregnancy	6 (1%)	3 (<1%)	3 (<1%)	--	--
Post abortion haemorrhage	2 (<1%)	1 (<1%)	1 (<1%)	--	--
Cephalo-pelvic disproportion	1 (<1%)	--	1 (<1%)	--	--
Premature labour	1 (<1%)	--	1 (<1%)	--	--
Retained products of conception	1 (<1%)	--	--	1 (<1%)	--
Vomiting in pregnancy	1 (<1%)	1 (<1%)	--	--	--
Psychiatric disorders	2 (<1%)	--	2 (<1%)	--	--
Intentional self-injury	2 (<1%)	--	2 (<1%)	--	--
Renal and urinary disorders	63 (6%)	60 (6%)	3 (<1%)	--	--
Proteinuria	36 (4%)	35 (3%)	1 (<1%)	--	--
Dysuria	16 (2%)	16 (2%)	--	--	--
Pollakiuria	7 (1%)	7 (1%)	--	--	--
Glycosuria	5 (<1%)	4 (<1%)	1 (<1%)	--	--
Haematuria	2 (<1%)	2 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Urine odour abnormal	2 (<1%)	2 (<1%)	--	--	--
Cystitis haemorrhagic	1 (<1%)	1 (<1%)	--	--	--
Urinary tract obstruction	1 (<1%)	--	1 (<1%)	--	--
Urinary tract pain	1 (<1%)	1 (<1%)	--	--	--
Reproductive system and breast disorders	72 (7%)	72 (7%)	--	--	--
Cervical dysplasia	18 (2%)	18 (2%)	--	--	--
Vaginal discharge	13 (1%)	13 (1%)	--	--	--
Vulvovaginal pruritus	10 (1%)	10 (1%)	--	--	--
Dysmenorrhoea	7 (1%)	7 (1%)	--	--	--
Cervix erythema	6 (1%)	6 (1%)	--	--	--
Menorrhagia	4 (<1%)	4 (<1%)	--	--	--
Pelvic pain	4 (<1%)	4 (<1%)	--	--	--
Cervical discharge	3 (<1%)	3 (<1%)	--	--	--
Cervical friability	2 (<1%)	2 (<1%)	--	--	--
Dyspareunia	2 (<1%)	2 (<1%)	--	--	--
Perineal ulceration	2 (<1%)	2 (<1%)	--	--	--
Vulval disorder	2 (<1%)	2 (<1%)	--	--	--
Vulvar erosion	2 (<1%)	2 (<1%)	--	--	--
Cervix disorder	1 (<1%)	1 (<1%)	--	--	--
Uterine pain	1 (<1%)	1 (<1%)	--	--	--
Vaginal disorder	1 (<1%)	1 (<1%)	--	--	--
Vaginal odour	1 (<1%)	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	Total	Moderate	Severe	Life threatening	Death
Vulval ulceration	1 (<1%)	1 (<1%)	--	--	--
Vulvovaginal pain	1 (<1%)	1 (<1%)	--	--	--
Vulvovaginal rash	1 (<1%)	1 (<1%)	--	--	--
Skin and subcutaneous tissue disorders	9 (1%)	9 (1%)	--	--	--
Dermatitis	2 (<1%)	2 (<1%)	--	--	--
Dermatitis atopic	2 (<1%)	2 (<1%)	--	--	--
Blister	1 (<1%)	1 (<1%)	--	--	--
Drug eruption	1 (<1%)	1 (<1%)	--	--	--
Rash	1 (<1%)	1 (<1%)	--	--	--
Rash macular	1 (<1%)	1 (<1%)	--	--	--
Rash maculo-papular	1 (<1%)	1 (<1%)	--	--	--
Vascular disorders	3 (<1%)	1 (<1%)	2 (<1%)	--	--
Hypertension	3 (<1%)	1 (<1%)	2 (<1%)	--	--

Table S7F. Creatinine Events by Randomization Arm and Severity Grade

Event Severity	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Participants Enrolled	5029	1007	1003	1009	1007	1003
Participants with one or more Creatinine Events	31 (0.6%)	4 (0.4%)	13 (1.3%)	2 (0.2%)	9 (0.9%)	3 (0.3%)
Total Number of Creatinine Events	38	5	16	2	12	3
Mild	37 (97%)	4 (80%)	16 (100%)	2 (100%)	12 (100%)	3 (100%)
Moderate	1 (3%)	1 (20%)	--	--	--	--
Severe	--	--	--	--	--	--
Life-threatening	--	--	--	--	--	--
Death	--	--	--	--	--	--

Table S7G. Severity Grade 3 or Higher, DAIDS EAE and ICH Serious Adverse Experiences by Treatment Arm

Body System (bold) and MedDRA Preferred Terms (indented)	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Participants Enrolled	5029	1007	1003	1009	1007	1003
Participants With One or More AE	525 (10%)	87 (9%)	123 (12%)	114 (11%)	93 (9%)	108 (11%)
Blood and lymphatic system disorders	32 (1%)	3 (<1%)	11 (1%)	9 (1%)	3 (<1%)	6 (1%)
Anaemia	9 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
Anaemia of pregnancy	5 (<1%)	--	2 (<1%)	2 (<1%)	1 (<1%)	--
Hypochromic anaemia	5 (<1%)	--	3 (<1%)	--	--	2 (<1%)
Lymph node pain	1 (<1%)	--	--	1 (<1%)	--	--
Lymphopenia	1 (<1%)	1 (<1%)	--	--	--	--
Microcytic anaemia	3 (<1%)	--	2 (<1%)	1 (<1%)	--	--
Neutropenia	4 (<1%)	1 (<1%)	--	2 (<1%)	--	1 (<1%)
Normochromic normocytic anaemia	3 (<1%)	--	1 (<1%)	1 (<1%)	--	1 (<1%)
Thrombocytopenia	1 (<1%)	--	--	1 (<1%)	--	--
Congenital, familial and genetic disorders	5 (<1%)	1 (<1%)	--	--	3 (<1%)	1 (<1%)
Congenital anomaly in offspring	5 (<1%)	1 (<1%)	--	--	3 (<1%)	1 (<1%)
Eye disorders	2 (<1%)	--	2 (<1%)	--	--	--
Keratoconus	1 (<1%)	--	1 (<1%)	--	--	--
Retinal detachment	1 (<1%)	--	1 (<1%)	--	--	--
Gastrointestinal disorders	21 (<1%)	--	4 (<1%)	7 (1%)	3 (<1%)	7 (1%)
Abdominal pain	2 (<1%)	--	--	1 (<1%)	--	1 (<1%)

Body System (bold) and MedDRA Preferred Terms (indented)	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Abdominal pain upper	2 (<1%)	--	1 (<1%)	--	1 (<1%)	--
Diarrhoea	7 (<1%)	--	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
Diarrhoea haemorrhagic	1 (<1%)	--	--	1 (<1%)	--	--
Food poisoning	1 (<1%)	--	--	--	--	1 (<1%)
Gastric ulcer	2 (<1%)	--	--	1 (<1%)	--	1 (<1%)
Gastritis	2 (<1%)	--	--	1 (<1%)	--	1 (<1%)
Nausea	2 (<1%)	--	--	1 (<1%)	--	1 (<1%)
Umbilical hernia	1 (<1%)	--	--	1 (<1%)	--	--
Vomiting	4 (<1%)	--	--	1 (<1%)	1 (<1%)	2 (<1%)
General disorders and administration site conditions	10 (<1%)	3 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)	--
Asthenia	2 (<1%)	1 (<1%)	--	1 (<1%)	--	--
Chest pain	1 (<1%)	--	--	1 (<1%)	--	--
Death	1 (<1%)	--	--	--	1 (<1%)	--
Fatigue	2 (<1%)	1 (<1%)	1 (<1%)	--	--	--
Oedema peripheral	2 (<1%)	2 (<1%)	--	--	--	--
Pain	1 (<1%)	1 (<1%)	--	--	--	--
Pyrexia	2 (<1%)	--	1 (<1%)	1 (<1%)	--	--
Suprapubic pain	1 (<1%)	--	--	--	1 (<1%)	--
Hepatobiliary disorders	3 (<1%)	--	--	2 (<1%)	1 (<1%)	--
Cholecystitis	2 (<1%)	--	--	1 (<1%)	1 (<1%)	--
Drug-induced liver injury	1 (<1%)	--	--	1 (<1%)	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Immune system disorders	1 (<1%)	--	--	--	--	1 (<1%)
Hypersensitivity	1 (<1%)	--	--	--	--	1 (<1%)
Infections and infestations	61 (1%)	5 (<1%)	9 (1%)	21 (2%)	12 (1%)	14 (1%)
Abdominal wall abscess	1 (<1%)	--	--	1 (<1%)	--	--
Acute tonsillitis	1 (<1%)	--	1 (<1%)	--	--	--
Appendicitis	4 (<1%)	--	--	2 (<1%)	1 (<1%)	1 (<1%)
Bartholin's abscess	2 (<1%)	--	--	2 (<1%)	--	--
Breast abscess	2 (<1%)	--	1 (<1%)	--	1 (<1%)	--
Disseminated tuberculosis	1 (<1%)	--	--	--	1 (<1%)	--
Dysentery	1 (<1%)	--	--	--	--	1 (<1%)
Gastroenteritis	7 (<1%)	--	1 (<1%)	4 (<1%)	1 (<1%)	1 (<1%)
Gastroenteritis bacterial	1 (<1%)	1 (<1%)	--	--	--	--
Genitourinary chlamydia infection	1 (<1%)	--	--	1 (<1%)	--	--
Gingival abscess	1 (<1%)	--	--	1 (<1%)	--	--
Malaria	5 (<1%)	--	1 (<1%)	1 (<1%)	3 (<1%)	--
Meningitis	1 (<1%)	--	--	--	1 (<1%)	--
Meningitis bacterial	1 (<1%)	--	1 (<1%)	--	--	--
Meningitis viral	1 (<1%)	--	--	--	--	1 (<1%)
Pelvic inflammatory disease	4 (<1%)	--	--	1 (<1%)	1 (<1%)	2 (<1%)
Pericarditis tuberculous	1 (<1%)	--	--	1 (<1%)	--	--
Pneumonia	1 (<1%)	--	--	1 (<1%)	--	--
Post procedural sepsis	1 (<1%)	--	--	--	1 (<1%)	--

Body System (bold) and MedDRA Preferred Terms (indented)	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Postoperative wound infection	1 (<1%)	1 (<1%)	--	--	--	--
Pulmonary tuberculosis	10 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	4 (<1%)
Pyelonephritis	2 (<1%)	--	--	--	1 (<1%)	1 (<1%)
Respiratory tract infection	2 (<1%)	--	1 (<1%)	--	--	1 (<1%)
Sinusitis	3 (<1%)	1 (<1%)	--	1 (<1%)	--	1 (<1%)
Skin infection	1 (<1%)	--	--	--	1 (<1%)	--
Staphylococcal infection	1 (<1%)	1 (<1%)	--	--	--	--
Tonsillitis	3 (<1%)	--	--	1 (<1%)	1 (<1%)	1 (<1%)
Tuberculosis	2 (<1%)	--	2 (<1%)	--	--	--
Vulval abscess	1 (<1%)	--	--	1 (<1%)	--	--
Wound sepsis	1 (<1%)	--	1 (<1%)	--	--	--
Injury, poisoning and procedural complications	27 (1%)	6 (1%)	9 (1%)	7 (1%)	5 (<1%)	--
Abdominal injury	1 (<1%)	--	--	--	1 (<1%)	--
Anaemia postoperative	1 (<1%)	--	1 (<1%)	--	--	--
Ankle fracture	3 (<1%)	1 (<1%)	--	1 (<1%)	1 (<1%)	--
Electric shock	1 (<1%)	--	--	--	1 (<1%)	--
Foreign body	1 (<1%)	--	1 (<1%)	--	--	--
Injury	3 (<1%)	--	1 (<1%)	1 (<1%)	1 (<1%)	--
Internal injury	1 (<1%)	--	--	1 (<1%)	--	--
Joint dislocation	2 (<1%)	--	2 (<1%)	--	--	--
Laceration	1 (<1%)	1 (<1%)	--	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Lower limb fracture	2 (<1%)	2 (<1%)	--	--	--	--
Overdose	1 (<1%)	--	1 (<1%)	--	--	--
Pelvic fracture	1 (<1%)	--	--	1 (<1%)	--	--
Soft tissue injury	1 (<1%)	--	1 (<1%)	--	--	--
Stab wound	1 (<1%)	--	--	1 (<1%)	--	--
Tendon injury	1 (<1%)	--	1 (<1%)	--	--	--
Thermal burn	5 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	--
Upper limb fracture	1 (<1%)	1 (<1%)	--	--	--	--
Investigations	63 (1%)	11 (1%)	14 (1%)	14 (1%)	10 (1%)	14 (1%)
Alanine aminotransferase increased	32 (1%)	6 (1%)	7 (1%)	7 (1%)	6 (1%)	6 (1%)
Aspartate aminotransferase increased	11 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)
Blood phosphorus decreased	6 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)	--
Blood pressure diastolic increased	1 (<1%)	--	--	--	--	1 (<1%)
Blood pressure increased	4 (<1%)	1 (<1%)	--	1 (<1%)	--	2 (<1%)
Blood pressure systolic increased	1 (<1%)	--	1 (<1%)	--	--	--
Haemoglobin decreased	9 (<1%)	--	2 (<1%)	3 (<1%)	2 (<1%)	2 (<1%)
Lymphocyte count decreased	1 (<1%)	--	--	1 (<1%)	--	--
Neutrophil count decreased	4 (<1%)	--	2 (<1%)	--	1 (<1%)	1 (<1%)
Metabolism and nutrition disorders	210 (4%)	45 (4%)	46 (5%)	26 (3%)	41 (4%)	52 (5%)
Abnormal loss of weight	103 (2%)	18 (2%)	27 (3%)	14 (1%)	19 (2%)	25 (2%)
Decreased appetite	1 (<1%)	--	--	1 (<1%)	--	--
Diabetes mellitus	13 (<1%)	4 (<1%)	4 (<1%)	2 (<1%)	--	3 (<1%)

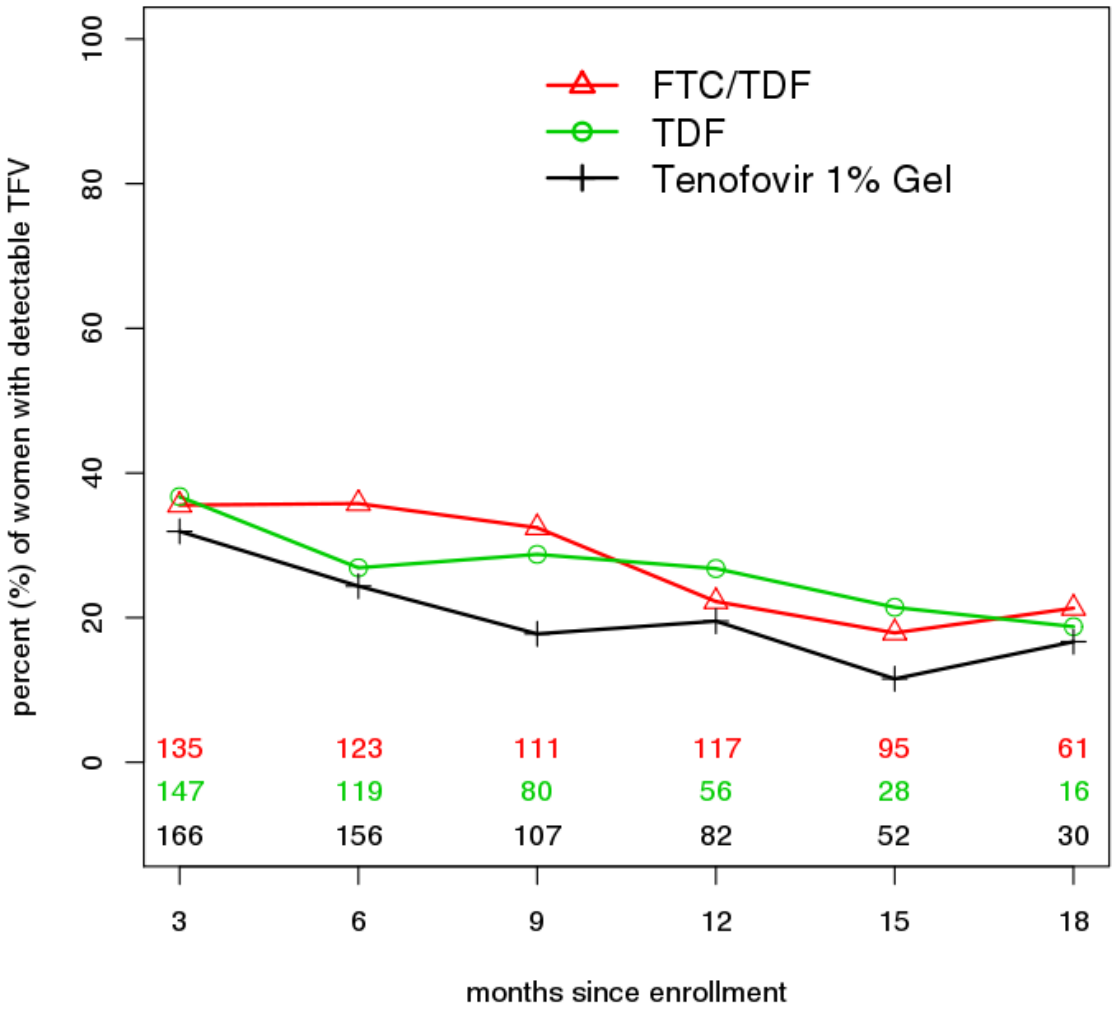
Body System (bold) and MedDRA Preferred Terms (indented)	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Hyperglycaemia	3 (<1%)	1 (<1%)	1 (<1%)	--	--	1 (<1%)
Hypophosphataemia	96 (2%)	23 (2%)	17 (2%)	10 (1%)	22 (2%)	24 (2%)
Type 2 diabetes mellitus	1 (<1%)	--	--	--	--	1 (<1%)
Musculoskeletal and connective tissue disorders	8 (<1%)	2 (<1%)	--	1 (<1%)	1 (<1%)	4 (<1%)
Arthralgia	2 (<1%)	1 (<1%)	--	1 (<1%)	--	--
Back pain	3 (<1%)	1 (<1%)	--	--	--	2 (<1%)
Musculoskeletal chest pain	1 (<1%)	--	--	--	1 (<1%)	--
Neck mass	1 (<1%)	--	--	--	--	1 (<1%)
Rheumatoid arthritis	1 (<1%)	--	--	--	--	1 (<1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (<1%)	--	--	2 (<1%)	1 (<1%)	--
Gliomatosis cerebri	1 (<1%)	--	--	1 (<1%)	--	--
Lipoma	1 (<1%)	--	--	1 (<1%)	--	--
Uterine leiomyoma	1 (<1%)	--	--	--	1 (<1%)	--
Nervous system disorders	24 (<1%)	5 (<1%)	7 (1%)	5 (<1%)	5 (<1%)	2 (<1%)
Cerebral infarction	1 (<1%)	1 (<1%)	--	--	--	--
Cerebrovascular accident	1 (<1%)	--	--	1 (<1%)	--	--
Convulsion	1 (<1%)	--	1 (<1%)	--	--	--
Dizziness	1 (<1%)	--	--	--	1 (<1%)	--
Epilepsy	1 (<1%)	--	--	1 (<1%)	--	--
Headache	11 (<1%)	2 (<1%)	3 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)

Body System (bold) and MedDRA Preferred Terms (indented)	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Loss of consciousness	1 (<1%)	--	1 (<1%)	--	--	--
Meningism	3 (<1%)	1 (<1%)	1 (<1%)	--	1 (<1%)	--
Migraine	2 (<1%)	--	1 (<1%)	1 (<1%)	--	--
Optic neuritis	1 (<1%)	--	--	--	--	1 (<1%)
Syncope	3 (<1%)	1 (<1%)	1 (<1%)	--	1 (<1%)	--
Transient ischaemic attack	2 (<1%)	--	1 (<1%)	1 (<1%)	--	--
Pregnancy, puerperium and perinatal conditions	49 (1%)	5 (<1%)	13 (1%)	14 (1%)	8 (1%)	9 (1%)
Abortion threatened	1 (<1%)	--	--	1 (<1%)	--	--
Cephalo-pelvic disproportion	1 (<1%)	--	--	--	--	1 (<1%)
Ectopic pregnancy	3 (<1%)	--	1 (<1%)	1 (<1%)	1 (<1%)	--
Haemorrhage in pregnancy	20 (<1%)	3 (<1%)	5 (<1%)	5 (<1%)	3 (<1%)	4 (<1%)
Hyperemesis gravidarum	2 (<1%)	--	1 (<1%)	--	1 (<1%)	--
Intrapartum haemorrhage	1 (<1%)	--	--	1 (<1%)	--	--
Post abortion haemorrhage	13 (<1%)	2 (<1%)	4 (<1%)	3 (<1%)	2 (<1%)	2 (<1%)
Postpartum haemorrhage	1 (<1%)	--	--	--	1 (<1%)	--
Pre-eclampsia	1 (<1%)	--	1 (<1%)	--	--	--
Premature labour	10 (<1%)	--	2 (<1%)	5 (<1%)	2 (<1%)	1 (<1%)
Premature rupture of membranes	2 (<1%)	--	--	2 (<1%)	--	--
Retained products of conception	2 (<1%)	--	--	1 (<1%)	--	1 (<1%)
Psychiatric disorders	12 (<1%)	--	5 (<1%)	3 (<1%)	2 (<1%)	2 (<1%)
Bipolar disorder	1 (<1%)	--	1 (<1%)	--	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Confusional state	1 (<1%)	--	--	--	1 (<1%)	--
Depression	2 (<1%)	--	1 (<1%)	--	1 (<1%)	--
Depression suicidal	1 (<1%)	--	--	1 (<1%)	--	--
Intentional self-injury	3 (<1%)	--	1 (<1%)	--	--	2 (<1%)
Suicidal ideation	1 (<1%)	--	1 (<1%)	--	--	--
Suicide attempt	4 (<1%)	--	2 (<1%)	2 (<1%)	--	--
Renal and urinary disorders	15 (<1%)	2 (<1%)	5 (<1%)	2 (<1%)	3 (<1%)	3 (<1%)
Glycosuria	7 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
Haematuria	2 (<1%)	--	1 (<1%)	--	1 (<1%)	--
Proteinuria	5 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	--	1 (<1%)
Urinary tract obstruction	1 (<1%)	--	--	--	--	1 (<1%)
Reproductive system and breast disorders	10 (<1%)	2 (<1%)	2 (<1%)	3 (<1%)	3 (<1%)	--
Bartholin's cyst	1 (<1%)	--	--	1 (<1%)	--	--
Breast discharge	1 (<1%)	--	--	--	1 (<1%)	--
Breast enlargement	1 (<1%)	--	--	--	1 (<1%)	--
Cervical dysplasia	1 (<1%)	1 (<1%)	--	--	--	--
Menorrhagia	3 (<1%)	--	1 (<1%)	1 (<1%)	1 (<1%)	--
Metrorrhagia	3 (<1%)	--	1 (<1%)	1 (<1%)	1 (<1%)	--
Pelvic pain	1 (<1%)	1 (<1%)	--	--	--	--
Respiratory, thoracic and mediastinal disorders	7 (<1%)	--	2 (<1%)	4 (<1%)	1 (<1%)	--
Asthma	4 (<1%)	--	2 (<1%)	2 (<1%)	--	--

Body System (bold) and MedDRA Preferred Terms (indented)	All Arms	TDF	FTC/TDF	Oral placebo	Tenofovir 1% Gel	Gel placebo
Dyspnoea	2 (<1%)	--	--	1 (<1%)	1 (<1%)	--
Epistaxis	1 (<1%)	--	--	1 (<1%)	--	--
Vascular disorders	22 (<1%)	4 (<1%)	6 (1%)	5 (<1%)	5 (<1%)	2 (<1%)
Deep vein thrombosis	1 (<1%)	1 (<1%)	--	--	--	--
Hypertension	19 (<1%)	3 (<1%)	5 (<1%)	5 (<1%)	4 (<1%)	2 (<1%)
Hypotension	2 (<1%)	--	1 (<1%)	--	1 (<1%)	--

Figure S1. Plasma Tenofovir Detection in a Random Cohort Sample of Participants in the Active Product Arms[1]



[1] FTC denotes emtricitabine, TFV tenofovir, and TDF tenofovir disoproxil fumarate

Figure S2. Algorithms for Determining HIV-1 Infection Status

Figure S2A. HIV Antibody Testing: Screening Algorithm

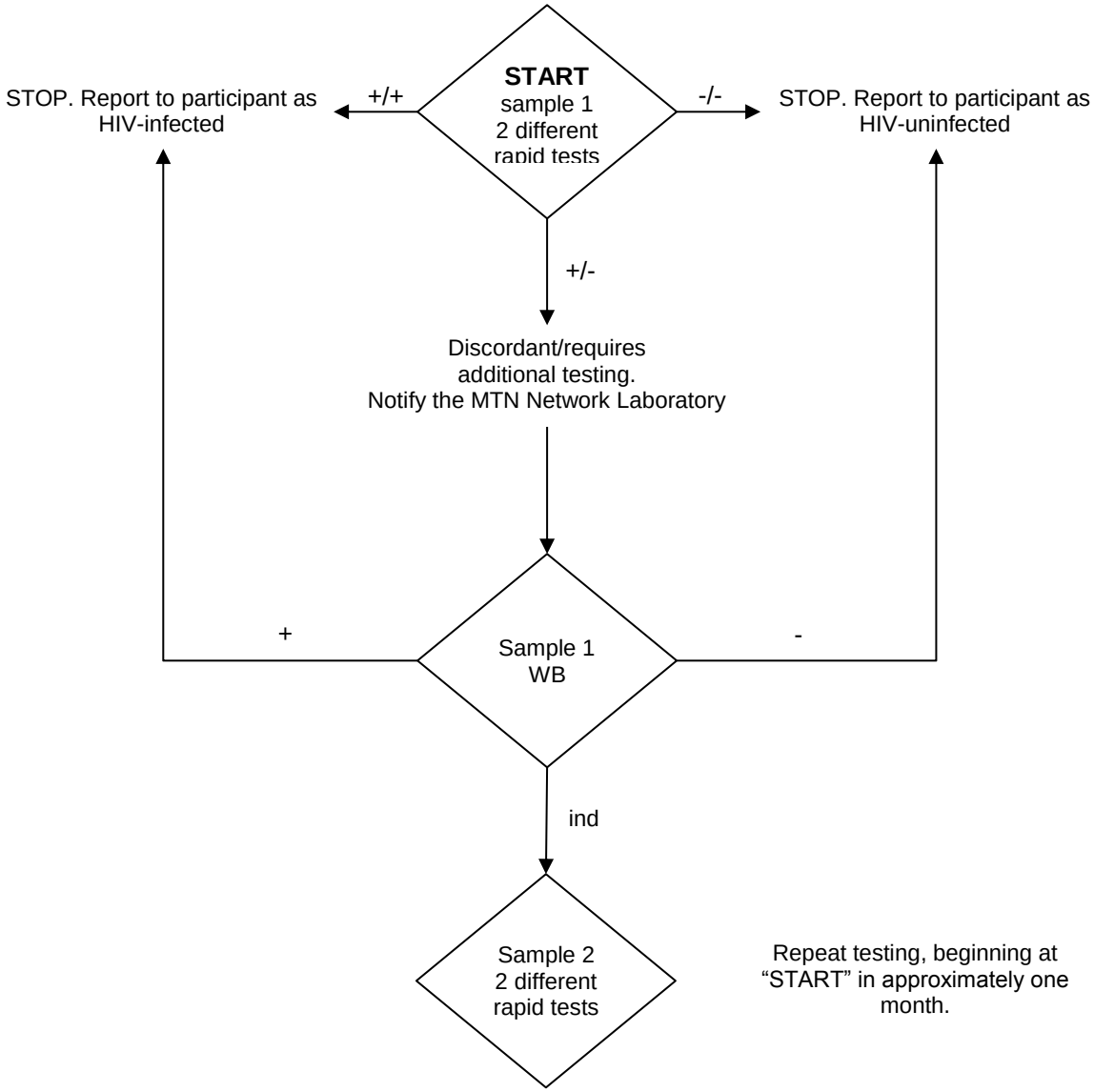


Figure S2B. Algorithm for HIV Antibody Testing: Follow-Up and Primary Endpoint Determination