Supplementary Appendix

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

Supplement to: Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. N Engl J Med 2016;375:2133-43. DOI: 10.1056/NEJMoa1602046

SUPPLEMENTARY TABLES AND FIGURES for IPM 027 (The Ring Study)

Article Title: Safety and Efficacy of Dapivirine Vaginal Ring for HIV Prevention in Women

Short Title: Dapivirine Vaginal Ring, HIV Prevention, Safety and Efficacy

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List of Supplementary Tables

Caption for Table S1. Eligibility Criteria for The Ring Study

Legend for Table S1. None.

Inclusion Criteria	**Participants had to meet all of the following criteria to be eligible for trial enrollment:** 1. Women ≥ 18 and ≤ 45 years of age, at screening, who can provide informed consent. 2. Available for all visits and consent to follow all procedures scheduled for the trial. 3. Self-reported sexually active (defined as an average of at least one penetrative penile-vaginal coital act per month for the last 3 months prior to screening). 4. HIV-negative as determined by the HIV algorithm applied at screening and enrollment. 5. On a stable form of contraception (defined as oral contraceptives, transdermal patches, long-acting injectable progestins, subcutaneous implants, intra-uterine devices or surgical sterilization), and willing to continue on stable contraception for the duration of the clinical trial, unless post-menopausal or surgically sterilized. 6. Asymptomatic for genital infections at the time of enrollment (if a woman is diagnosed with any clinically significant treatable STI, she must have initiated treatment at least 1 week prior to enrollment and have completed the full course of treatment). 7. Willing to provide adequate locator information for trial retention purposes and be reachable per local standard procedures (e.g., by home visit or telephone; or via family or close neighbor contacts); confidentiality to be maintained. 8. Willing to refrain from participation in another research trial using drugs, vaccines, medical devices, microbicides, or oral pre-exposure prophylaxis investigational drugs for the duration of The Ring Study.

Exclusion Criteria	**Participants who met any of the following criteria were not enrolled:** 1. Currently pregnant or last pregnancy within 3 months prior to screening or intends to become pregnant during trial participation. 2. Currently breast-feeding. 3. Non-therapeutic injection drug use in the 12 months prior to screening. 4. Participated in another research trial using drugs, medical devices, microbicides or oral pre-exposure prophylaxis agents within 60 days prior to screening. 5. Previously participated or currently participating in any HIV vaccine trial. 6. Untreated, clinically significant urogenital infections, e.g., urinary tract, or other sexually transmitted infections, or other gynecological symptoms within 1 week prior to enrollment. 7. Has a Grade 2 or higher pelvic examination finding, according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies. 8. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, diagnosed chronic and/or recurrent vulvovaginal candidiasis urethral obstruction, incontinence or urge incontinence. 9. Any gynecological surgery within 90 days prior to screening. 10. Any Grade 1 or higher baseline aspartate aminotransferase (AST), alanine transaminase (ALT), or platelet count, and any Grade 2 or higher baseline hematology, chemistry or urinalysis laboratory value according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

	11. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or a silicone elastomer. 12. Any history of diabetes mellitus and chronic use of oral corticosteroid therapy; and any uncontrolled serious chronic or progressive disease. 13. Cervical cytology at screening that requires cryotherapy, biopsy or treatment (other than for infection). Women with Grade 1 cervical cytology findings can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology). 14. Any condition(s) that, in the opinion of the investigator, might put the participant at risk, or interfere with the trial objectives or the participant's adherence to trial requirements.

Caption for Table S2: Flow Chart of Clinical Procedures in The Ring Study

Legend for Table S2:

[a.] All visits while on investigational product could occur ± 7 days of scheduled visits.

[b.] Enrollment could occur the same day as Screening 2.

[c.] The informed consent was signed prior to screening and again prior to enrollment.

[d.] Directed examination determined by symptomatology.

[e.] If a vaginal ring was removed for more than 24 hours, a new ring could be dispensed.

[f.] The diary card could be reviewed at 4-weekly visits as part of the adherence assessment. Participants could consult their diary cards during adherence counselling.

[g.] The baseline acceptability questionnaire was administered only at Week 4.

[h.] Six to 10 participants and male partners were invited to participate in an individual interview to be held during weeks 24 to 42 after center activation. Each research center also conducted two to three focus groups with participants and 6 to 10 individual interviews with male partners who completed the Last Product Use Visit.

[i.] If the investigational product was permanently discontinued due to a laboratory adverse event, safety assessment(s) were performed at the Exit Visit if the laboratory abnormality had not resolved.

Year 1 Visits	**Screening 1**	**Screening 2**	**Enrollment[b]**	**4-weekly**	**12-weekly**	**24-weekly[h]**	**Last Product Use[h]**	**As Needed**	**Exit Visit**
Trial Weeks[a]	**Screening 2 had to occur within 28 days of Screening 1**			**Weeks 4 - 52**	**Weeks 12, 24, 36, 48**	**Weeks 24, 48**			
Informed Consent[c]	X		X						
Assign Participant Identification number	X								
Comprehension Assessment			X						
Demographics	X								
Medical History	X	X							
Concomitant Medication Evaluation	X	X		X	X	X	X		X
Inclusion/Exclusion Criteria	X	X							
Locator Information	X	X		X	X	X	X		X
Menses Information	X	X		X	X	X	X		
Physical Examination	X	X[d]					X	X[d]	
Adverse Event Evaluation			X	X	X	X	X	X	X[l]
Pelvic Examination	X	X			X	X	X	X	

Vaginal Ring Dispensing and Insertion			X	X	X	X		X[e]	
Vaginal Ring Removal/Return				X	X	X	X	X[e]	
Provision and Collection of Diary Card			X[f]	X[f]	X[f]	X[f]			
Provision of Male Condoms	X	X		X	X	X	X	X	X
Collection of Diary Card				X[f]	X[f]	X[f]	X[f]		
Adherence Questionnaire				X	X	X	X		
Acceptability Questionnaire				X[g]		X	X		
Behavioral Questionnaire			X						
HIV/STI Risk Reduction Counselling	X	X		X	X	X	X		X
Vaginal Ring Adherence Counselling			X	X	X	X		X	
Contraceptive Counselling	X		X	X	X	X	X	X	X
HIV Pre- & Post-Test Counselling	X	X		X	X	X	X	X	X
Year 2 Visits				**4-weekly**	**12-weekly**	**24-weekly**	**Last Product Use[h]**	**As Needed**	**Exit Visit**

Trial Weeks[a]				**Weeks 56 - 100**	**Weeks 60, 72, 84, 96**	**Weeks 72, 96**	**Week 104/ Early discontinuation**		
Concomitant Medication Evaluation				X	X	X	X		X
Locator Information				X	X	X	X		X
Menses Information				X	X	X	X		
Physical Examination							X	X[d]	
Adverse Event Evaluation				X	X	X	X	X	X[l]
Pelvic Examination					X	X	X	X	
Vaginal Ring Dispensing and Insertion				X	X	X		X[e]	
Vaginal Ring Removal/Return				X	X	X	X	X[e]	
Provision and Collection of Diary Card				X	X	X			
Provision of Male Condoms				X	X	X	X	X	X
Adherence Questionnaire				X	X	X	X		
Acceptability Questionnaire						X	X		
HIV/STI Risk Reduction Counselling				X	X	X	X		X

Vaginal Ring Adherence Counselling				X	X	X		X	
Contraceptive Counselling				X	X	X	X	X	X
HIV Pre- & Post-Test Counselling				X	X	X	X	X	X

Caption for Table S3: Flow Chart of Laboratory Procedures in The Ring Study

Legend for Table S3:

[j.] Sample was stored and only tested after confirmation of seroconversion.

[k.] Sample was obtained at the time of 2 positive HIV rapid tests, and tested subsequently or after confirmation of seroconversion.

[l.] Urinalysis dipstick testing (urine microscopy only if indicated), hematology (full blood count with differential count and platelets), chemistry (electrolytes, calcium, urea, creatinine, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], bilirubin).

[m.] Blood samples for viral genotyping were only collected at the scheduled Exit Visit following seroconversion.

[n.] Treponema pallidum hemagglutination test (TPHA)/treponema pallidum particle agglutination assay (TPPA) was performed if RPR positive.

[o.] A confirmatory serum pregnancy test could be requested if a false positive urine pregnancy test was suspected.

[p.] For women with Grade 1 cervical cytology findings, cervical cytology was repeated according to the local standard of care, or after 6 months; whichever was more conservative.

[q.] Blood samples for herpes simplex virus type 2 (HSV-2) serology, HIV viral genotyping and HIV-RNA PCR were collected at Screening 2 for research centers that use this option.

[r.] It was recommended that cervical cytology only be repeated 6 weeks post-collection of previous sample.

Year 1 Visits	**Screening 1**	**Screening 2**	**Enrollment**	**4-weekly**	**12-weekly**	**Annual**	**Last Product Use**	**As Needed**	**Exit Visit**

Trial Weeks				**Weeks 4 - 52**	**Weeks 12, 24, 36, 48**	**Week 52**			
Urine Pregnancy Test[o]	X	X		X	X	X	X	X	
HIV Rapid Test	X	X		X	X	X	X		X
HIV-RNA PCR Test			X[j,q]	X[j]	X[j]	X[j]	X[j]		
Plasma Dapivirine Levels				X[j,k]	X[j,k]	X[j,k]	X[j,k]		
Vaginal Fluid Dapivirine Levels				X[j,k]	X[j,k]	X[j,k]	X[j,k]		
Plasma Viral Genotype Sample			X[j,q]	X[j,k]	X[j,k]	X[j,k]	X[j,k]		X[m]
HSV-2 Serology			X[j,q]	X[j,k]	X[j,k]	X[j,k]	X[j,k]		
Laboratory Testing for Safety Assessments[k]	X				X		X	X	
Vaginal Fluid pH and Vaginal Flora Sample			X		X		X		
Cervicovaginal Sample Collection for STI Tests	X				X		X	X	
Cervical Sample Collection for Cytology[p]	X					X	X[r]		
Rapid Plasma Reagin (RPR)[n]	X						X	X	
Final Laboratory Results Provided to Participants									X

Year 2 Visits	**Screening 1**	**Screening 2**	**Enrollment**	**4-weekly**	**12-weekly**	**Last Product Use**	**As Needed**	**Exit Visit**
Trial Weeks				**Weeks 56 - 100**	**Weeks 60, 72, 84, 96**	**Week 104/ Early discontinuation**		
Urine Pregnancy Test[o]				X	X	X	X	
HIV Rapid Test				X	X	X		X
HIV-RNA PCR Test				X[j]	X[j]	X[j]		
Plasma Dapivirine Levels				X[j,k]	X[j,k]	X[j,k]		
Vaginal Fluid Dapivirine Levels				X[j,k]	X[j,k]	X[j,k]		
Plasma Viral Genotype Sample				X[j,k]	X[j,k]	X[j,k]		X[m]
HSV-2 serology				X[j,k]	X[j,k]	X[j,k]		
Laboratory Testing for Safety Assessments[l]					X	X	X	
Vaginal Fluid pH and Vaginal Flora Sample					X	X		
Cervicovaginal Sample Collection for STI Tests					X	X	X	
Cervical Sample Collection for Cytology						X[r]		
RPR[n]						X	X	

Final Laboratory Results Provided to Participants								X

Caption for Table S4: HIV-1 Drug Resistance Mutations Among HIV-1 Seroconverters (Confirmed Trial Endpoints) (m-ITT Population)

Legend for Table S4: The percentage calculation is based on the total number of participants in m-ITT (a) or who HIV-1 seroconverted (b).

Classification based on the Stanford Database.

NRTI = Nucleoside Reverse Transcriptase Inhibitor; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitor; PI=Protease Inhibitor.

	DVR-004 n (%)	**Placebo n (%)**
Overall		
Participants enrolled	1300 (100.0%)	650 (100.0%)
Participants who HIV seroconverted (confirmed trial endpoints)(a)	77 (5.9%)	56 (8.6%)
Participants with HIV-1 Drug Resistance Mutations (b):	30 (39.0%)	24 (42.9%)
NNRTI Resistance Mutation	14 (18.2%)	9 (16.1%)
E138A	9 (11.7%)	1 (1.8%)
A98G	3 (3.9%)	1 (1.8%)
K103N	3 (3.9%)	2 (3.6%)
K101E	1 (1.3%)	1 (1.8%)
V106M	1 (1.3%)	1 (1.8%)
V090I	0	4 (7.1%)
V108I	0	1 (1.8%)
E138Q	0	1 (1.8%)
Y181C	0	1 (1.8%)
Y188C	0	1 (1.8%)
H221Y	0	1 (1.8%)
NRTI Resistance Mutation	1 (1.3%)	0
PI Major Resistance Mutation	2 (2.6%)	0
PI Minor Resistance Mutation	20 (26.0%)	17 (30.4%)

Caption for Table S5: Adherence Based on Residual Levels of Dapivirine in Used Rings and Corresponding Plasma Concentrations by Trial Visit (m-ITT Population)

Legend for Table S5: N = number of participants with data (residual level of used ring and/or plasma concentration); n = number of participants within adherence category.

Adherent = ring residual level ≤ 23.5 mg and plasma concentration ≥ 95 pg/mL (if both assessments are available, otherwise based on the available assessment).

Non-adherent = ring residual level > 23.5 mg or plasma concentration < 95 pg/mL.

Trial Week	**Adherent n/N (%)**	**Non-adherent n/N (%)**
Trial week 4	993/1269 (78.3%)	276/1269 (21.7%)
Trial week 8	961/1251 (76.8%)	290/1251 (23.2%)
Trial week 12	929/1232 (75.4%)	303/1232 (24.6%)
Trial week 16	905/1206 (75.0%)	301/1206 (25.0%)
Trial week 20	880/1187 (74.1%)	307/1187 (25.9%)
Trial week 24	865/1164 (74.3%)	299/1164 (25.7%)
Trial week 28	855/1159 (73.8%)	304/1159 (26.2%)
Trial week 32	850/1149 (74.0%)	299/1149 (26.0%)
Trial week 36	856/1139 (75.2%)	283/1139 (24.8%)
Trial week 40	864/1132 (76.3%)	268/1132 (23.7%)
Trial week 44	854/1117 (76.5%)	263/1117 (23.5%)
Trial week 48	849/1093 (77.7%)	244/1093 (22.3%)
Trial week 52	812/1038 (78.2%)	226/1038 (21.8%)
Trial week 56	761/973 (78.2%)	212/973 (21.8%)
Trial week 60	735/915 (80.3%)	180/915 (19.7%)
Trial week 64	710/867 (81.9%)	157/867 (18.1%)
Trial week 68	678/806 (84.1%)	128/806 (15.9%)
Trial week 72	619/747 (82.9%)	128/747 (17.1%)
Trial week 76	586/703 (83.4%)	117/703 (16.6%)
Trial week 80	535/668 (80.1%)	133/668 (19.9%)

Trial Week	**Adherent** **n/N (%)**	**Non-adherent** **n/N (%)**
Trial week 84	511/642 (79.6%)	131/642 (20.4%)
Trial week 88	503/621 (81.0%)	118/621 (19.0%)
Trial week 92	484/600 (80.7%)	116/600 (19.3%)
Trial week 96	485/589 (82.3%)	104/589 (17.7%)
Trial week 100	463/571 (81.1%)	108/571 (18.9%)
Trial week 104	437/550 (79.5%)	113/550 (20.5%)

Caption for Table S6. Incidence of Grade 3 or 4 Treatment-Emergent Adverse Events (Regardless of Causality)

Legend for Table S6. TEAE=treatment-emergent adverse event.

AEs were coded using version 15.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Medical and gynecological conditions were classified by System Organ Class (SOC) and Preferred Term (PT).

P-value for difference in incidence rate of Grade 3 or 4 TEAEs = 0.0617 (continuity adjusted Chi-square, df = 1).

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Any Grade 3 or 4 TEAE (worst grade)	63 (4.8%)	19 (2.9%)
Investigations	*16 (1.2%)*	*6 (0.9%)*
Blood phosphorus decreased	8 (0.6%)	3 (0.5%)
Grade 3	8 (0.6%)	3 (0.5%)
Haemoglobin decreased	2 (0.2%)	2 (0.3%)
Grade 3	2 (0.2%)	2 (0.3%)
Alanine aminotransferase increased	2 (0.2%)	0
Grade 3	2 (0.2%)	0
Aspartate aminotransferase increased	1 (0.1%)	1 (0.2%)
Grade 3	1 (0.1%)	1 (0.2%)
Blood potassium increased	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Blood pressure increased	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Weight decreased	1 (0.1%)	0
Grade 3	1 (0.1%)	0

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Infections and infestations	*11 (0.8%)*	*5 (0.8%)*
Amoebic dysentery	1 (0.1%)	1 (0.2%)
Grade 3	1 (0.1%)	1 (0.2%)
Gastroenteritis	2 (0.2%)	0
Grade 3	2 (0.2%)	0
Malaria	2 (0.2%)	0
Grade 3	2 (0.2%)	0
Acute tonsillitis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Cellulitis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Cystitis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Herpes zoster	0	1 (0.2%)
Grade 3	0	1 (0.2%)
Injection site abscess	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Pelvic inflammatory disease	0	1 (0.2%)
Grade 3	0	1 (0.2%)
Pulmonary tuberculosis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Pyelonephritis	0	1 (0.2%)
Grade 3	0	1 (0.2%)
Respiratory tract infection	0	1 (0.2%)
Grade 3	0	1 (0.2%)
Subcutaneous abscess	1 (0.1%)	0

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Grade 3	1 (0.1%)	0
Reproductive system and breast disorders	*9 (0.7%)*	*5 (0.8%)*
Coital bleeding	4 (0.3%)	2 (0.3%)
Grade 3	4 (0.3%)	2 (0.3%)
Cervical dysplasia	4 (0.3%)	1 (0.2%)
Grade 3	4 (0.3%)	1 (0.2%)
Female genital tract fistula	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Metrorrhagia	0	1 (0.2%)
Grade 3	0	1 (0.2%)
Pelvic pain	0	1 (0.2%)
Grade 3	0	1 (0.2%)
Injury, poisoning and procedural complications	*6 (0.5%)*	*0*
Accidental overdose	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Alcohol poisoning	1 (0.1%)	0
Grade 4	1 (0.1%)	0
Animal bite	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Head injury	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Human bite	1 (0.1%)	0
Grade 3	1 (0.1%)	0

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Radius fracture	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Ulna fracture	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Pregnancy, puerperium and perinatal conditions	*5 (0.4%)*	*1 (0.2%)*
Abortion spontaneous	5 (0.4%)	1 (0.2%)
Grade 3	5 (0.4%)	1 (0.2%)
Nervous system disorders	*4 (0.3%)*	*0*
Headache	3 (0.2%)	0
Grade 3	3 (0.2%)	0
Presyncope	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Gastrointestinal disorders	*2 (0.2%)*	*1 (0.2%)*
Diarrhoea haemorrhagic	2 (0.2%)	1 (0.2%)
Grade 3	2 (0.2%)	1 (0.2%)
Metabolism and nutrition disorders	*3 (0.2%)*	*0*
Diabetes mellitus	3 (0.2%)	0
Grade 3	3 (0.2%)	0
Vascular disorders	*3 (0.2%)*	*0*
Hypertension	2 (0.2%)	0

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Grade 3	2 (0.2%)	0
Deep vein thrombosis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Blood and lymphatic system disorders	*2 (0.2%)*	*0*
Anaemia	2 (0.2%)	0
Grade 3	2 (0.2%)	0
Musculoskeletal and connective tissue disorders	*2 (0.2%)*	*0*
Myalgia	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Pain in extremity	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Psychiatric disorders	*1 (0.1%)*	*1 (0.2%)*
Major depression	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Suicide attempt	0	1 (0.2%)
Grade 3	0	1 (0.2%)
Hepatobiliary disorders	*1 (0.1%)*	*0*
Cholecystitis acute	1 (0.1%)	0
Grade 3	1 (0.1%)	0

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*1 (0.1%)*	*0*
Acral lentiginous melanoma stage unspecified	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Renal and urinary disorders	*1 (0.1%)*	*0*
Urinary retention	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Respiratory, thoracic and mediastinal disorders	*1 (0.1%)*	*0*
Pulmonary embolism	1 (0.1%)	0
Grade 4	1 (0.1%)	0

Caption for Table S7: Treatment-Emergent Adverse Events (Regardless of Causality) with an Incidence of > 5% in either Treatment Arm

Legend for Table S7: * This term described events where there was a clinical suspicion of genital infection and syndromic treatment given but no etiology was confirmed.

TEAE=treatment-emergent adverse event.

AEs were coded using version 15.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Medical and gynecological conditions were classified by System Organ Class (SOC) and Preferred Term (PT).

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Any TEAE (worst grade)	1142 (87.4%)	559 (85.7%)
Infections and infestations	*987 (75.6%)*	*487 (74.7%)*
Gynaecological chlamydia infection	400 (30.6%)	205 (31.4%)
Grade 2	400 (30.6%)	205 (31.4%)
Genital infection female*	287 (22.0%)	115 (17.6%)
Grade 1	69 (5.3%)	27 (4.1%)
Grade 2	218 (16.7%)	88 (13.5%)
Genitourinary tract gonococcal infection	234 (17.9%)	106 (16.3%)
Grade 2	234 (17.9%)	106 (16.3%)
Upper respiratory tract infection	225 (17.2%)	109 (16.7%)
Grade 1	108 (8.3%)	48 (7.4%)
Grade 2	117 (9.0%)	61 (9.4%)
Trichomoniasis	217 (16.6%)	95 (14.6%)
Grade 2	217 (16.6%)	95 (14.6%)
Urinary tract infection	180 (13.8%)	97 (14.9%)
Grade 1	96 (7.4%)	48 (7.4%)
Grade 2	84 (6.4%)	49 (7.5%)

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Vulvovaginal candidiasis	165 (12.6%)	76 (11.7%)
Grade 1	58 (4.4%)	31 (4.8%)
Grade 2	107 (8.2%)	45 (6.9%)
Vulvovaginitis	114 (8.7%)	68 (10.4%)
Grade 1	88 (6.7%)	50 (7.7%)
Grade 2	26 (2.0%)	18 (2.8%)
Vaginitis bacterial	96 (7.4%)	39 (6.0%)
Grade 1	11 (0.8%)	7 (1.1%)
Grade 2	85 (6.5%)	32 (4.9%)
Viral rhinitis	67 (5.1%)	32 (4.9%)
Grade 1	67 (5.1%)	32 (4.9%)
Nasopharyngitis	64 (4.9%)	29 (4.4%)
Grade 1	51 (3.9%)	22 (3.4%)
Grade 2	13 (1.0%)	7 (1.1%)
Malaria	60 (4.6%)	30 (4.6%)
Grade 1	2 (0.2%)	1 (0.2%)
Grade 2	56 (4.3%)	29 (4.4%)
Grade 3	2 (0.2%)	0
Reproductive system and breast disorders	*608 (46.6%)*	*306 (46.9%)*
Metrorrhagia	335 (25.7%)	182 (27.9%)
Grade 1	302 (23.1%)	160 (24.5%)
Grade 2	33 (2.5%)	21 (3.2%)
Grade 3	0	1 (0.2%)
Menorrhagia	124 (9.5%)	64 (9.8%)
Grade 1	79 (6.0%)	45 (6.9%)

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Grade 2	45 (3.4%)	19 (2.9%)
Menometrorrhagia	82 (6.3%)	40 (6.1%)
Grade 1	44 (3.4%)	20 (3.1%)
Grade 2	38 (2.9%)	20 (3.1%)
Dysmenorrhoea	78 (6.0%)	43 (6.6%)
Grade 1	62 (4.7%)	35 (5.4%)
Grade 2	16 (1.2%)	8 (1.2%)
Cervical dysplasia	73 (5.6%)	44 (6.7%)
Grade 1	41 (3.1%)	24 (3.7%)
Grade 2	28 (2.1%)	19 (2.9%)
Grade 3	4 (0.3%)	1 (0.2%)
Gastrointestinal disorders	*256 (19.6%)*	*149 (22.9%)*
Diarrhoea	56 (4.3%)	39 (6.0%)
Grade 1	38 (2.9%)	27 (4.1%)
Grade 2	18 (1.4%)	12 (1.8%)
Musculoskeletal and connective tissue disorders	*192 (14.7%)*	*82 (12.6%)*
Myalgia	68 (5.2%)	35 (5.4%)
Grade 1	56 (4.3%)	28 (4.3%)
Grade 2	11 (0.8%)	7 (1.1%)
Grade 3	1 (0.1%)	0
Arthralgia	71 (5.4%)	31 (4.8%)
Grade 1	65 (5.0%)	29 (4.4%)
Grade 2	6 (0.5%)	2 (0.3%)

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Nervous system disorders	*135 (10.3%)*	*88 (13.5%)*
Headache	100 (7.7%)	70 (10.7%)
Grade 1	60 (4.6%)	51 (7.8%)
Grade 2	37 (2.8%)	19 (2.9%)
Grade 3	3 (0.2%)	0

Caption for Table S8. Incidence of Serious Adverse Events (Regardless of Causality)

Legend for Table S8. TEAE=treatment-emergent adverse event.

AEs were coded using version 15.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Medical and gynecological conditions were classified by System Organ Class (SOC) and Preferred Term (PT).

P-value for difference in incidence rate of serious TEAEs = 0.0084 (continuity adjusted Chi-square, df = 1).

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Any serious TEAE (worst grade)	38 (2.9%)	6 (0.9%)
Infections and infestations	*15 (1.1%)*	*1 (0.2%)*
Febrile infection	3 (0.2%)	0
Grade 2	3 (0.2%)	0
Malaria	3 (0.2%)	0
Grade 2	1 (0.1%)	0
Grade 3	2 (0.2%)	0
Acute tonsillitis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Bronchitis	1 (0.1%)	0
Grade 2	1 (0.1%)	0
Cellulitis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Cystitis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Gastroenteritis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Hepatitis B	1 (0.1%)	0

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Grade 1	1 (0.1%)	0
Injection site abscess	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Pneumonia	1 (0.1%)	0
Grade 2	1 (0.1%)	0
Pulmonary tuberculosis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Respiratory tract infection	0	1 (0.2%)
Grade 3	0	1 (0.2%)
Injury, poisoning and procedural complications	*8 (0.6%)*	*0*
Gunshot wound	2 (0.2%)	0
Grade missing	1 (0.1%)	0
Grade 5	1 (0.1%)	0
Accidental overdose	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Alcohol poisoning	1 (0.1%)	0
Grade 4	1 (0.1%)	0
Fibula fracture	1 (0.1%)	0
Grade 2	1 (0.1%)	0
Forearm fracture	1 (0.1%)	0
Grade 2	1 (0.1%)	0
Multiple injuries	1 (0.1%)	0
Grade 5	1 (0.1%)	0
Radius fracture	1 (0.1%)	0

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Grade 3	1 (0.1%)	0
Tibia fracture	1 (0.1%)	0
Grade 2	1 (0.1%)	0
Ulna fracture	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Reproductive system and breast disorders	*3 (0.2%)*	*3 (0.5%)*
Cervical dysplasia	3 (0.2%)	1 (0.2%)
Grade 2	3 (0.2%)	1 (0.2%)
Breast mass	0	1 (0.2%)
Grade 2	0	1 (0.2%)
Menometrorrhagia	1 (0.1%)	0
Grade 2	1 (0.1%)	0
Metrorrhagia	0	1 (0.2%)
Grade 3	0	1 (0.2%)
Nervous system disorders	*3 (0.2%)*	*0*
Headache	3 (0.2%)	0
Grade 3	3 (0.2%)	0
Hepatobiliary disorders	*2 (0.2%)*	*0*
Cholecystitis acute	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Cholelithiasis	1 (0.1%)	0
Grade 2	1 (0.1%)	0

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Pregnancy, puerperium and perinatal conditions	*2 (0.2%)*	*0*
Abortion spontaneous	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Ectopic pregnancy	1 (0.1%)	0
Grade 2	1 (0.1%)	0
Vascular disorders	*1 (0.1%)*	*1 (0.2%)*
Circulatory collapse	0	1 (0.2%)
Grade 5	0	1 (0.2%)
Deep vein thrombosis	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Eye disorders	*1 (0.1%)*	*0*
Photophobia	1 (0.1%)	0
Grade 2	1 (0.1%)	0
Gastrointestinal disorders	*1 (0.1%)*	*0*
Gastrointestinal pain	1 (0.1%)	0
Grade 2	1 (0.1%)	0
General disorders and administration site conditions	*1 (0.1%)*	*0*
Pyrexia	1 (0.1%)	0
Grade 2	1 (0.1%)	0

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Musculoskeletal and connective tissue disorders	*1 (0.1%)*	*0*
Pain in extremity	1 (0.1%)	0
Grade missing	1 (0.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*1 (0.1%)*	*0*
Acral lentiginous melanoma stage unspecified	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Psychiatric disorders	*0*	*1 (0.2%)*
Suicide attempt	0	1 (0.2%)
Grade 3	0	1 (0.2%)
Renal and urinary disorders	*1 (0.1%)*	*0*
Urinary retention	1 (0.1%)	0
Grade 3	1 (0.1%)	0
Respiratory, thoracic and mediastinal disorders	*1 (0.1%)*	*0*
Pulmonary embolism	1 (0.1%)	0
Grade 4	1 (0.1%)	0
Skin and subcutaneous tissue disorders	*1 (0.1%)*	*0*
Skin ulcer	1 (0.1%)	0
Grade 2	1 (0.1%)	0

Caption for Table S9. Incidence of Product-Related Treatment-Emergent Adverse Events (as Assessed by the Investigator)

Legend for Table S9. TEAE=treatment-emergent adverse event.

AEs were coded using version 15.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Medical and gynecological conditions were classified by System Organ Class (SOC) and Preferred Term (PT).

MedDRA System Organ Class **Dictionary-derived Term** **Severity**	**DVR-004** **n (%)**	**Placebo** **n (%)**
Any product-related TEAE	5 (0.4%)	3 (0.5%)
Reproductive system and breast disorders	*4 (0.3%)*	*2 (0.3%)*
Metrorrhagia	2 (0.2%)	0
Grade 1	2 (0.2%)	0
Pelvic discomfort	1 (0.1%)	1 (0.2%)
Grade 1	1 (0.1%)	1 (0.2%)
Menometrorrhagia	0	1 (0.2%)
Grade 1	0	1 (0.2%)
Pelvic pain	1 (0.1%)	0
Grade 1	1 (0.1%)	0
General disorders and administration site conditions	*1 (0.1%)*	*1 (0.2%)*
Application site pain	0	1 (0.2%)
Grade 1	0	1 (0.2%)
Suprapubic pain	1 (0.1%)	0
Grade 1	1 (0.1%)	0

Caption for Table S10: Incidence Rate of Sexually Transmitted Infections

Legend for Table S10: STI rate determined by laboratory test results.

(a) Person-years are based on the cumulative follow-up time (from enrollment to trial completion/discontinuation).

	DVR-004 N=1306	**Placebo N=652**
Person-years of follow-up time (years) (a)	2033.83	989.11
STI Test: Time to any STI		
Number of participants with events	651 (49.8%)	308 (47.2%)
Incidence rate (per 100 person-years)	32.01	31.14
95% confidence interval for incidence rate (per 100 person years)	29.55 to 34.47	27.66 to 34.62
STI Test: Time to Chlamydia		
Number of participants with events	411 (31.5%)	209 (32.1%)
Incidence rate (per 100 person-years)	20.21	21.13
95% confidence interval for incidence rate (per 100 person years)	18.25 to 22.16	18.27 to 23.99
STI Test: Time to Neisseria gonorrhoeae		
Number of participants with events	250 (19.1%)	110 (16.9%)
Incidence rate (per 100 person-years)	12.29	11.12
95% confidence interval for incidence rate (per 100 person years)	10.77 to 13.82	9.04 to 13.20
STI Test: Time to Syphilis TPHA/TPPA		
Number of participants with events	17 (1.3%)	5 (0.8%)
Incidence rate (per 100 person-years)	0.84	0.51

	DVR-004 **N=1306**	**Placebo** **N=652**
95% confidence interval for incidence rate (per 100 person years)	0.44 to 1.23	0.06 to 0.95
STI Test: Time to Trichomonas		
Number of participants with events	222 (17.0%)	101 (15.5%)
Incidence rate (per 100 person-years)	10.92	10.21
95% confidence interval for incidence rate (per 100 person years)	9.48 to 12.35	8.22 to 12.20

List of Supplementary Figures

(uploaded separately to maintain image quality)

Caption for Figure S1. HIV-1 testing algorithm at Screening 1

Legend for Figure S1. None.

Caption for Figure S2. HIV-1 testing algorithm at Screening 2 and Enrollment

Legend for Figure S2. None.

Caption for Figure S3. HIV-1 testing algorithm at Trial Visits

Legend for Figure S3 None.

Caption for Figure S4. HIV-1 testing algorithm at Last Product Use Visit

Legend for Figure S4. None.

Caption for Figure S5. HIV-1 testing algorithm at Exit Visit (6 Weeks after Product Use)

Legend for Figure S5. None.

Caption for Figure S6. Overview of Efficacy Results

Legend for Figure S6. P-values for the primary and complementary analyses are for the hypothesis of any evidence of efficacy (i.e. testing against a null hypothesis of 0%); P-values for the subgroup analysis correspond to a test for significant interaction in the site-stratified Cox proportional-hazards model.

m-ITT=modified intent-to-treat.

Figure S1. HIV-1 testing algorithm at Screening 1

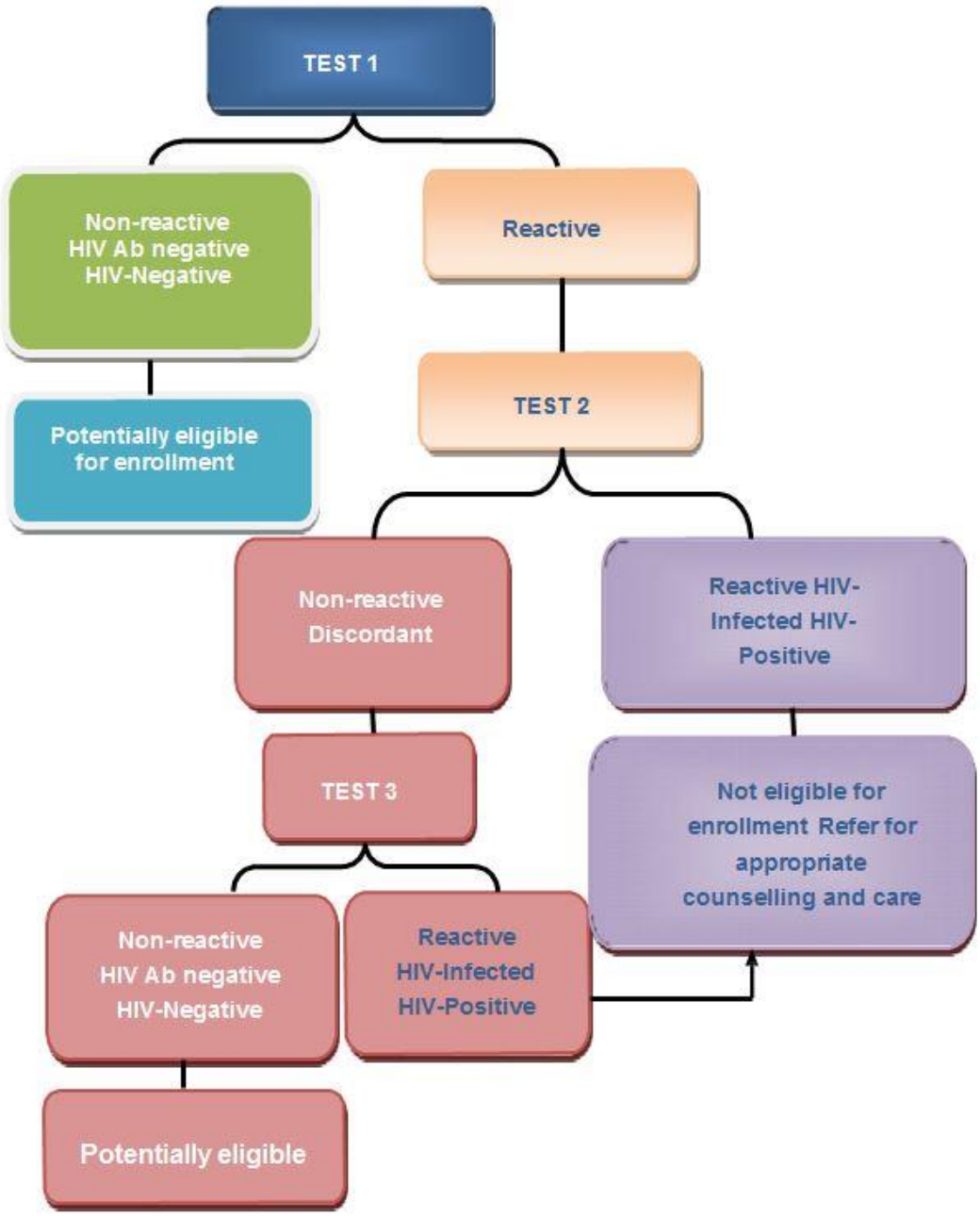

Figure S2. HIV-1 testing algorithm at Screening 2 and Enrollment

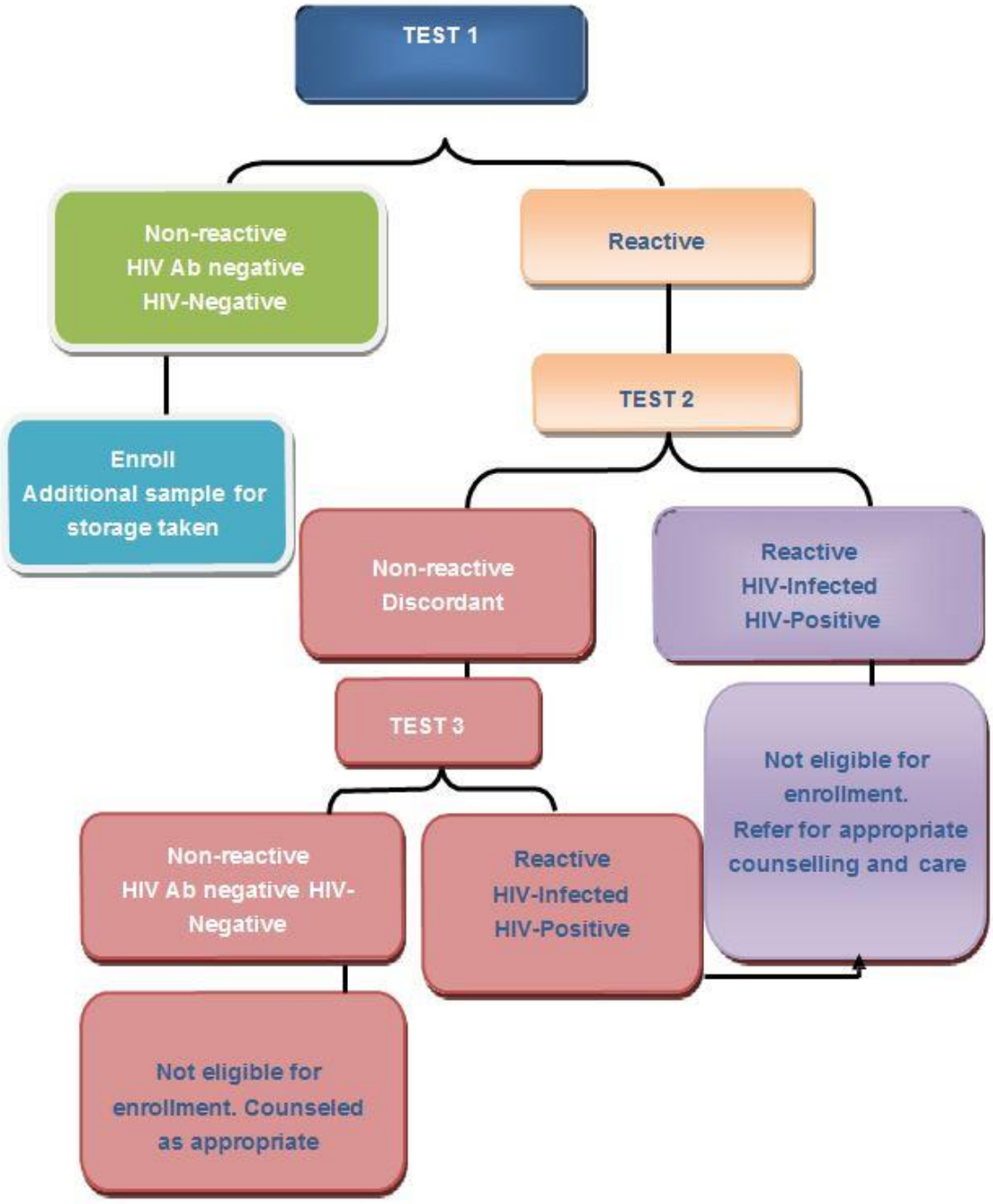

Figure S3. HIV-1 testing algorithm at Trial Visits

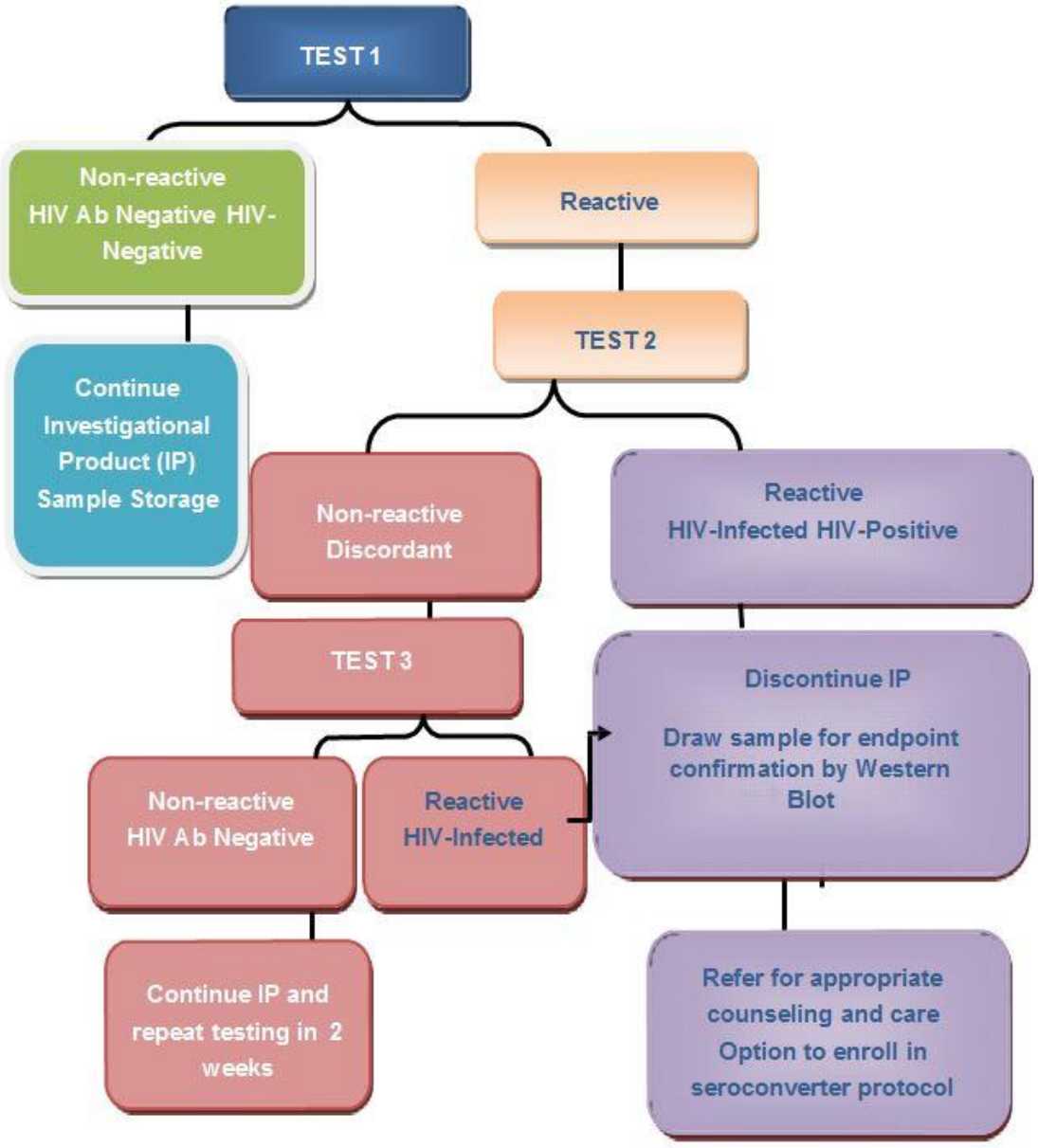

Figure S4. HIV-1 testing algorithm at Last Product Use Visit

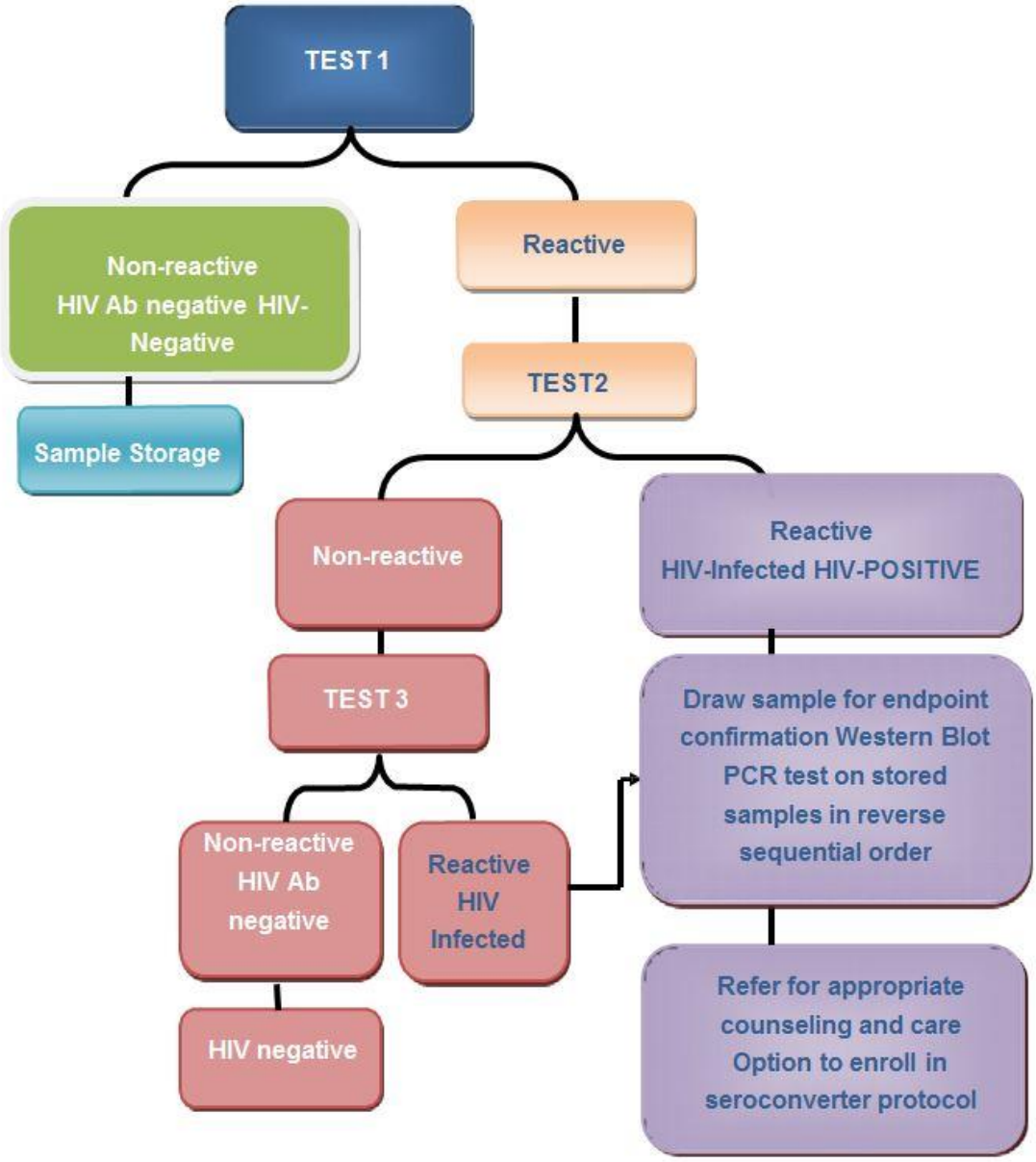

Figure S5. HIV-1 testing algorithm at Exit Visit (6 Weeks after Product Use)

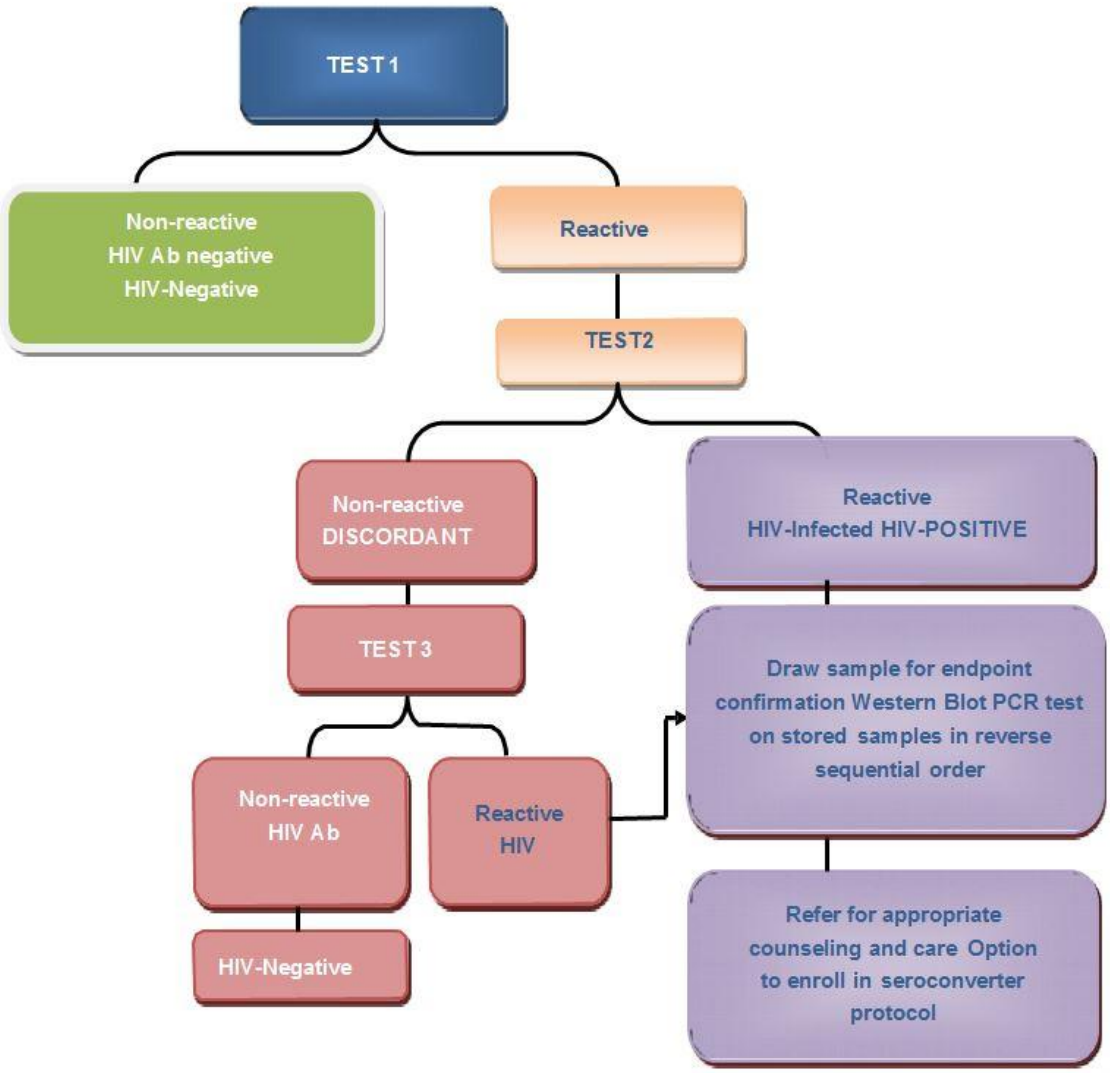

Figure S6. Overview of Efficacy Results